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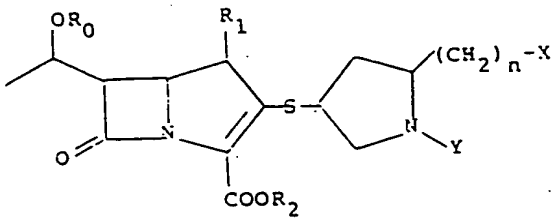
(54) Carbapenem compounds and production thereof.

(57) A compound of the formula:



wherein R_1 is a hydrogen atom or a lower alkyl group, R_2 is a hydrogen atom or a conventional protecting group for a carboxyl group, R_0 is a hydrogen atom or a conventional protecting group for a hydroxyl group, X is a protected or unprotected amino group, a carboxyl group, a lower alkoxy-carbonyl group, an ar(lower)alkyloxycarbonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower alkylthio group, a lower alkylsulfonyl group or a group of either one of the following formulas:

(1) $-CON\begin{matrix}R_3\\R_4\end{matrix}$

wherein R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, or they are taken together to represent an alkylene chain to form, in combination with the adjacent nitrogen atom, a 3- to 7-membered cyclic amino group,

(2) $-ZCOR_5$

wherein Z represents -NH— or -O- and R_5 represents an amino group, a mono(lower)alkylamino group, a di(lower)alkylamino group, a lower alkyloxy group or a lower alkyl group,

(3) $-NH-\underset{\underset{R_6}{|}}{C}=NH$

wherein R_6 represents a hydrogen atom or a lower alkyl group,

(4) $-CH=N-R_7$

wherein R_7 represents a mono(lower)alkylamino group, a di(lower)alkylamino group or a lower alkyloxy group, or

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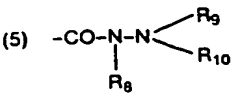
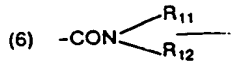
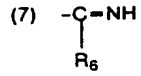
(5) 

wherein R_8, R_9 and R_{10}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, Y represents a hydrogen atom, a conventional protecting group for an amino group or a group of either one of the following formulas:

(6) 

wherein R_{11} and R_{12}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group or

(7) 

wherein R_6 is as defined above and n is an integer of 1 to 6, and a pharmacologically acceptable salt thereof, which is useful as an antimicrobial agent.

Our Ref: U 144 EP
Sumitomo Pharmaceuticals Company, Limited
Case: 610911

0182213

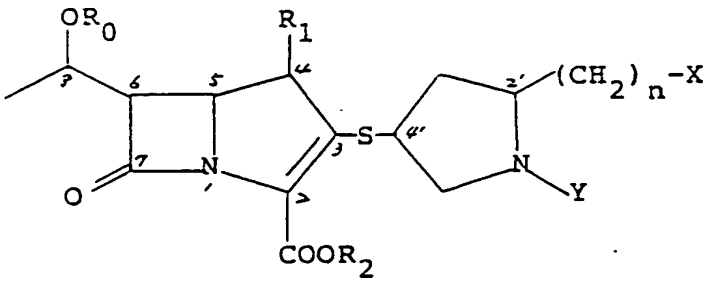
November 7, 1985

CARBAPENEM COMPOUNDS AND PRODUCTION THEREOF

The present invention relates to novel carbapenem compounds useful as antimicrobial agents or intermediates therefor, and their production.

Since the discovery of thienamycin having a potential antimicrobial activity against Gram-negative and Gram-positive bacteria, studies on syntheses of carbapenem derivatives which are analogous to thienamycin have been widely developed. As a result, it has now been found that carbapenem derivatives having, as their 2-side chain, a substituent easily derived from 4-hydroxy-proline, i.e. a pyrrolidinyl group substituted on its 2-position, exhibit a potential antimicrobial activity and are useful as medicines or as intermediates for antibiotic substances.

This invention provides novel carbapenem compounds of the formula (I):



(I)

wherein

R_1 is a hydrogen atom or a lower alkyl group;

R_2 is a hydrogen atom or a conventional protecting group for a carboxyl group;

R_0 is a hydrogen atom or a conventional protecting group for a hydroxyl group;

X is a protected or unprotected amino group, a carboxyl group, a lower alkoxycarbonyl group, an ar(lower)-alkyloxycarbonyl group such as phenyl(lower)alkyloxy-carbonyl, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower alkylthio group, a lower alkylsulfonyl group or a group of either one of the following formulas:

(1) $-CON\begin{matrix}R_3\\R_4\end{matrix}$

wherein R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, or they are taken together to represent an alkylene chain to form, in combination with the adjacent nitrogen atom, a 3- to 7-membered cyclic amino group,

(2) $-ZCOR_5$

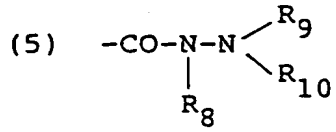
wherein Z represents -NH- or -O- and R_5 represents an amino group, a mono(lower)alkylamino group, a di(lower)alkylamino group, a lower alkyloxy group or a lower alkyl group,

(3) $-NH-\underset{\displaystyle R_6}{\overset{\displaystyle |}{C}}=NH$

wherein R_6 represents a hydrogen atom or a lower alkyl group,

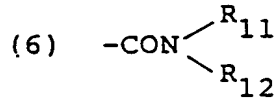
(4) $-CH=N-R_7$

wherein R_7 represents a mono(lower)alkylamino group, a di(lower)alkylamino group or a lower alkyloxy group, or

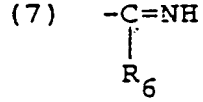
(5) 

wherein R_8, R_9 and R_{10}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group;

Y is a hydrogen atom, a conventional protecting group for an amino group or a group of either one of the following formulas:

(6) 

wherein R_{11} and R_{12}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, or

(7) 

wherein R_6 is as defined above; and

n is an integer of 1 to 6.

The invention also provides the pharmacologically acceptable salts of said carbapenem compounds (I).

In the above formula (I), the term "lower" as used in connection with any group is intended to mean generally a group having not more than 8 carbon atoms, particularly not more than 5 carbon atoms, unless otherwise defined. For instance, specific examples of lower alkyl are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, etc. Further, for instance, specific examples of lower alkyloxy are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, t-butoxy, etc.

The protecting group for a hydroxyl group as

represented by R_0 may be any of those commonly employed, and its preferred examples are C_1-C_4 alkoxycarbonyl (e.g. t-butyloxycarbonyl), halo(C_1-C_3)alkoxycarbonyl (e.g. 2-iodoethyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl), substituted or unsubstituted ar(lower)alkyloxycarbonyl such as substituted or unsubstituted phenyl(C_1-C_3)alkyloxycarbonyl (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl), tri-(C_1-C_4)alkylsilyl (e.g. trimethylsilyl, t-butyldimethylsilyl), etc.

The protecting group for a carboxyl group as represented by R_2 may be any of those commonly employed, and its preferred examples include C_1-C_4 alkyl (e.g. methyl, ethyl, isopropyl, t-butyl), halo(C_1-C_3)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl), C_1-C_4 alkoxymethyl (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl), C_1-C_8 aliphatic acyloxymethyl (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl), 1-(C_1-C_4)-alkoxycarbonyloxyethyl (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycorbonyloxyethyl), substituted or unsubstituted ar(lower)alkyl such as substituted or unsubstituted phenyl(C_1-C_3)alkyl (e.g. benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl), benzhydryl, phthalidyl, etc.

In the definitions for R_1, X and Y, the term "lower" is preferred to mean any group having not more than 3 carbon atoms. For instance, examples of lower alkyl are methyl, ethyl, n-propyl and isopropyl.

When X is the group (1), R_3 and R_4 may be the same

or different from each other. In the definitions for R_3 and R_4, the lower alkyl group represents preferably the one having not more than 4 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl).

In the case where R_3 and R_4 jointly represent an alkylene chain to form, in combination with the adjacent nitrogen atom, a 3- to 7-membered cyclic amino group, specific examples include a saturated cyclic amino group (e.g. aziridino, azetidino, pyrrolidino, piperidino).

The lower alkoxycarbonyl group for X includes, for example, C_1-C_4 alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl and isopropoxycarbonyl. The ar(lower)-alkyloxycarbonyl group for X includes, for example, substituted or unsubstituted ar(lower)alkyloxycarbonyl such as benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl and o-nitrobenzyloxycarbonyl.

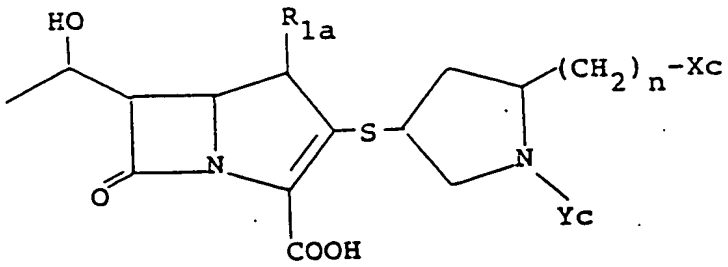
When Y is the group (6), the lower alkyl group represented by R_{11} or R_{12} is preferred to have 1 to 4 carbon atoms and may be, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, etc.

The protecting group for an amino group as represented by Y or used in the protected amino group of X may be any of those commonly employed. Preferred examples are C_1-C_4 alkoxycarbonyl (e.g. t-butyloxycarbonyl), halo-(C_1-C_3)alkoxycarbonyl (e.g. 2-iodoethyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl), substituted or unsubstituted ar(lower)alkyloxycarbonyl such as substituted or unsubstituted phenyl(C_1-C_3)alkyloxycarbonyl (e.g. benzyloxy-

carbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl), tri(C_1-C_4)alkylsilyl (e.g. trimethylsilyl, t-butyldimethylsilyl), etc.

The carbapenem compounds (I) wherein $-COOR_2$ or X represents a carboxyl group may be converted into their pharmacologically acceptable salts, if desired. Specific examples of such salts are inorganic metal salts (e.g. lithium salt, sodium salt, potassium salt, calcium salt, magnesium salt), ammonium salts (e.g. ammonium salt, cyclohexylammonium salt, diisopropylammonium salt, triethylammonium salt), etc., among which sodium salt and potassium salt are the most preferred. The carbapenem compounds (I) wherein X represents an amino group or a group of the formula (3) or Y represents a hydrogen atom or a group of the formula (7) may be also converted into their pharmacologically acceptable salts, if desired. Examples of such salts are those with mineral acids such as hydrochloric acid and sulfuric acid.

Among the carbapenem compounds (I) of the invention, preferred are those of the formula (I-a):

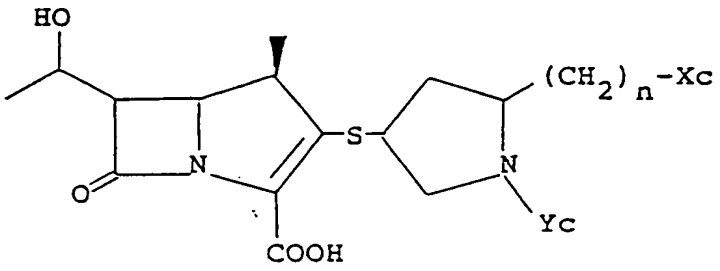


(I-a)

wherein R_{1a} is a hydrogen atom or a lower alkyl group, Xc is either one of the groups (1) to (5), an amino group, a

carboxyl group, a lower alkoxycarbonyl group, a cyano group, a hydroxyl group, a lower alkoxy group, a lower alkylthio group or a lower alkylsulfonyl group, Yc is a hydrogen atom or either one of the groups (6) and (7) and n is an integer of 1 to 6.

Particularly preferred are the carbapenem compounds of the formula (I-b):



(I-b)

wherein Xc and Yc are each as defined above.

Preferred examples of the substituent: $-(CH_2)_n-Xc$ at the 2-position of the pyrrolidinyl group include those of the following formulas (a) to (e):

(a) $-(CH_2)_nCON\begin{matrix}R_3\\R_4\end{matrix}$

$-CH_2CON\begin{matrix}R_3\\R_4\end{matrix}$, $-CH_2CH_2CON\begin{matrix}R_3\\R_4\end{matrix}$,

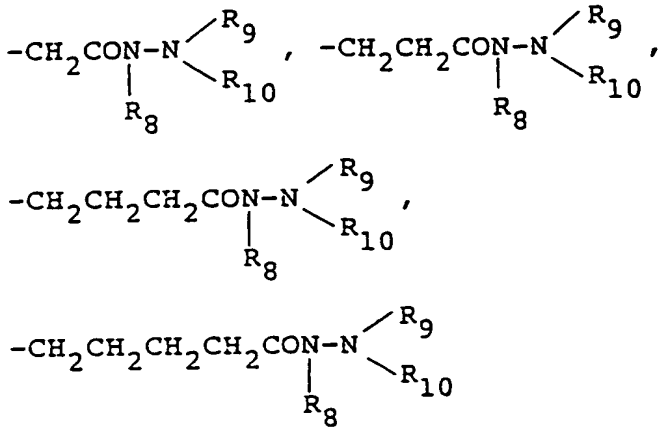
$-CH_2CH_2CH_2CON\begin{matrix}R_3\\R_4\end{matrix}$, $-CH_2CH_2CH_2CH_2CON\begin{matrix}R_3\\R_4\end{matrix}$

(b) $-(CH_2)_nCH=N-R_7$

$-CH_2CH=N-R_7$, $-CH_2CH_2CH=N-R_7$,

$-CH_2CH_2CH_2CH=N-R_7$, $-CH_2CH_2CH_2CH_2CH=N-R_7$

(c) $-(CH_2)_nCON(R_8)-N\begin{matrix}R_9\\R_{10}\end{matrix}$



(d) $-(CH_2)_nOR_{13}$

$-CH_2OR_{13}$, $-CH_2CH_2OR_{13}$, $-CH_2CH_2CH_2OR_{13}$,

$-CH_2CH_2CH_2CH_2OR_{13}$

(e) $-(CH_2)_nCOOR_{13}$

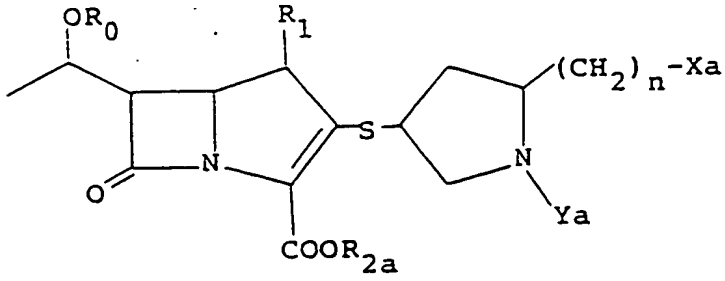
$-CH_2COOR_{13}$, $-CH_2CH_2COOR_{13}$, $-CH_2CH_2CH_2COOR_{13}$,

$-CH_2CH_2CH_2CH_2COOR_{13}$

wherein R_3, R_4, R_7, R_8, R_9 and R_{10} are each as defined above and R_{13} represents a hydrogen atom or a lower alkyl group, the groups (a) and (d) being particularly favorable.

The carbapenem compounds (I) can be produced by various procedures, among which some typical ones are set forth below.

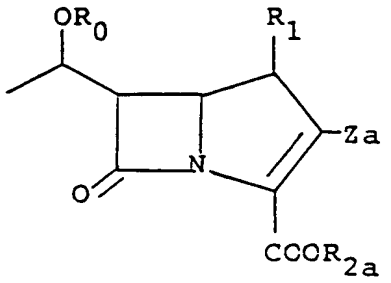
(A) The carbapenem compound of the formula (II):



(II)

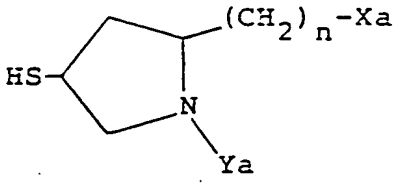
wherein R_0, R_1 and n are each as defined above, R_{2a} is a protecting group for a carboxyl group, Xa is either one of

the groups (1), (2), (4) and (5), a protected amino group, a lower alkoxycarbonyl group, an ar(lower)alkyoxycabonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower alkylthio group or a lower alkylsulfonyl group and Ya is a protecting group for an amino group or the group (6), is prepared by reacting the carbapenem compound of the formula (III):



(III)

wherein R_0, R_1 and R_{2a} are each as defined above and Za is a reactive ester group with a mercaptan of the formula (IV):



(IV)

wherein Xa, Ya and n are each as defined above, in an inert solvent in the presence of a base.

The term "reactive ester group" herein used is intended to mean a leaving group such as a halide or a sulfonate. It may be the residue of a substituted or unsubstituted arylsulfonate, a lower alkanesulfonate, a halo(lower)alkanesulfonate, a diarylphosphoric acid ester, a halide or the like. Examples of the substituted or unsubstituted arylsulfonate are benzenesulfonate, p-toluenesulfonate, p-nitrobenzenesulfonate, p-bromobenzenesulfonate,

etc. Examples of the lower alkanesulfonate are methanesulfonate, ethanesulfonate, etc. Examples of the halo(lower)alkanesulfonate are trifluoromethanesulfonate, etc. As the diarylphosphoric acid ester, there may be exemplified diphenylphosphoric acid ester, etc. The halide includes, for example, chloride, bromide, iodide, etc. Of these reactive esters, preferred are p-toluenesulfonate, methanesulfonate, diphenylphosphoric acid ester, etc.

The protecting group for a carboxyl group as represented by R_{2a} corresponds to the one as represented by R_2, and the same preferred groups as enumerated for R_2 can also be applied to R_{2a}.

In said process, the carbapenem compound (III) and the mercaptan (IV) are reacted normally by the use of a large excessive amount, particularly from 1 to 1.5 equivalents, of the latter to the former.

As the inert solvent, there may be used dioxane, tetrahydrofuran, dimethylformamide, dimethylsulfoxide, acetonitrile, hexamethylphosphoramide, etc. Their mixtures are also usable. Among them, acetonitrile, dimethylformamide, etc. are preferred. Examples of the base include inorganic bases (e.g. sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, potassium t-butoxide) and organic bases (e.g. pyridine, 4-dimethylaminopyridine, triethylamine, diisopropylethylamine), among which organic bases are preferred. The base may be used in such an amount as sufficient to proceed the reaction and usually from 1 to 1.5 equivalents per mol of the mercaptan (IV).

The reaction can be carried out at a temperature of from about -78 to 60°C, preferably from -40 to 40°C.

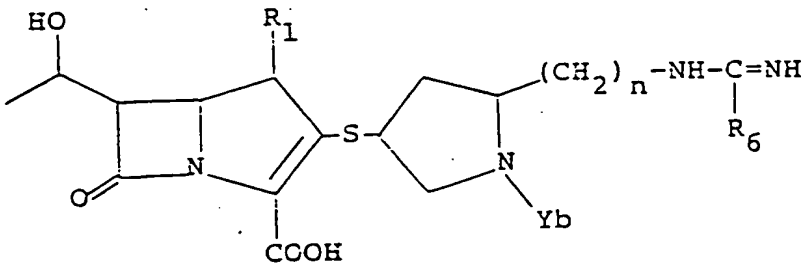
Recovery of the reaction product from the reaction mixture may be accomplished by a per se conventional procedure, for instance, by washing the reaction mixture with water, drying and evaporating the solvent. The reaction product may, if necessary, be further purified by a per se conventional means, for example, by recrystallization, preparative thin layer chromatography, column chromatography or the like.

The thus obtained carbapenam compound (II) may be subjected, if necessary, to reaction for removal of the hydroxyl-protecting group on R_0, removal of the amino-protecting group on Ya, removal of the carboxyl-protecting group on R_{2a} and/or removal of the protecting group on Xa to obtain the carbapenem compound (I). Removal of the protecting group may be achieved by adoption of an appropriate per se conventional procedure depending upon the type of the protecting group. For instance, the carbapenem compound (II) bearing a halo(lower)alkoxycarbonyl group or an ar(lower)alkyloxycarbonyl group as the hydroxyl-protecting group or the amino-protecting group or a halo(lower)alkyl group, an ar(lower)alkyl group or a benzhydryl group as the carboxyl-protecting group may be subjected to reduction for removal of any of those protecting groups. The reduction is preferably carried out, for instance, by treatment with zinc in an organic solvent (e.g. acetic acid, tetrahydrofuran, methanol) in the case where the protecting group is a

halo(lower)alkoxycarbonyl group or a halo(lower)alkyl group, or by catalytic reduction using a catalyst (e.g. platinum, palladium-on-carbon) in the case where the protecting group is an ar(lower)alkyloxycarbonyl group, an ar(lower)alkyl group or a benzhydryl group. The catalytic reduction is usually effected in any liquid medium chosen from organic solvents such as lower alcohols (e.g. methanol, ethanol), ethers (e.g. tetrahydrofuran, dioxane) and acetic acid or from their mixtures with water or buffer solutions (e.g. phosphoric acid, morpholinopropanesulfonic acid). The reduction is normally conducted at a temperature of from about 0 to 100°C, preferably from about 0 to 40°C, in a hydrogen atmosphere under the atmospheric or elevated pressure.

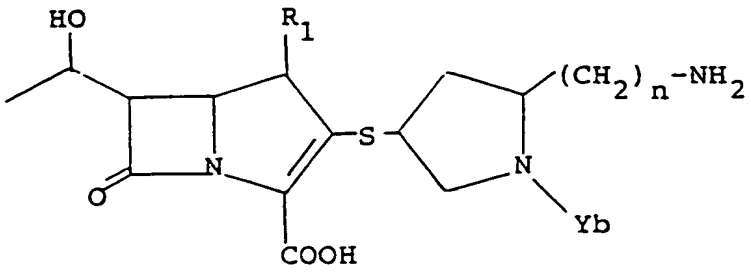
When the protecting group is an o-nitrobenzyl group or an o-nitrobenzyloxycarbonyl group, it can also be removed by photo-reaction.

(B) The carbapenem compound of the formula (V):



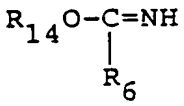
(V)

wherein R_1 and n are each as defined above, R_6 is a hydrogen atom or a lower alkyl group and Yb is the group (6) can be prepared by reacting the carbapenem compound of the formula (VI):



(VI)

wherein R_1, Yb and n are each as defined above with an imine of the formula (8):



(8)

wherein R_6 is as defined above and R_{14} represents a lower alkyl group or a benzyl group, or a salt thereof under a basic condition.

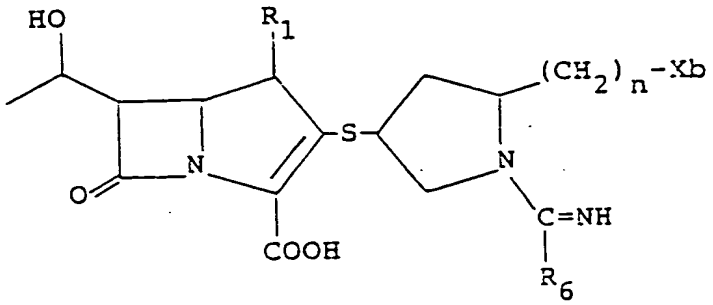
In the formula (8), the lower alkyl group for R_{14} may be preferably alkyl of 1 to 5 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl). As the salt of the imine (8), there are exemplified hydrohalides such as hydrochloride, hydrobromide and hydroiodide.

The reaction is normally effected under a basic condition at a pH ranging from about 8 to 14, preferably from about 9 to 10. Such basic condition may be prepared by the use of an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide), an alkaline earth metal hydroxide (e.g. calcium hydroxide, barium hydroxide), an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate), etc. The reaction is preferably carried out in water, but can be done in a mixed solvent of water with an organic solvent chosen from lower alcohols (e.g. methanol, ethanol, n-

propanol), ethers (e.g. tetrahydrofuran, dioxane), dimethylformamide, acetonitrile, etc. The reaction temperature is preferred to be from 0°C to room temperature, but the reaction rate may be suppressed or promoted by cooling or heating if necessary.

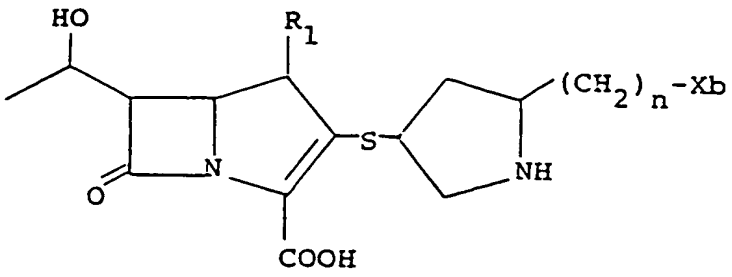
Separation of the reaction product from the reaction mixture may be accomplished by a per se conventional procedure. For example, the reaction mixture is neutralized with a conventional acid (e.g. hydrochloric acid, sulfuric acid) and purified by column chromatography on an adsorbent to give a fraction containing the desired product. Concentration or lyophilization of the fraction affords the reaction product.

(C) The carbapenem compound of the formula (VII):



(VII)

wherein R_1, R_6 and n are each as defined above, Xb is either one of the groups (1), (2), (4) and (5), a carboxyl group, a lower alkoxycarbonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower alkylthio group or a lower alkylsulfonyl group, can be prepared by reacting a carbapenem compound of the formula (VIII):



(VIII)

wherein R_1, Xb and n are each as defined above with the imine (8) or its salt under a basic condition by the same procedure as (B).

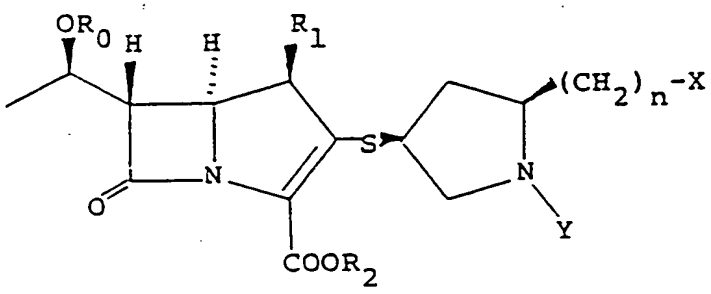
In the carbapenem compounds (I), asymmetric carbon atoms are present at the 5-, 6- and 8-positions. The carbon atoms at the 2'- and 4'-positions in the 2-side chain are also asymmetric. Further, when R_1 is an alkyl group, the carbon atom at the 4-position is asymmetric. Therefore, the carbapenem compounds (I) have optical isomers and steric isomers due to these asymmetric carbon atoms. Although all of these isomers are represented by a respective single formula for the sake of convenience, the scope of the invention extends to and covers all of them.

Among those isomers, preferred are the ones having the same relative-configuration as thienamycin on the carbon atom at the 5-position. The compounds wherein R_1 is an alkyl group and which have a 5S-configuration, i.e. the (5S,6S)- or (5S,6S)-compounds, are preferred. The compounds wherein R_1 is a hydrogen atom and which have a 5R-configuration, i.e. the (5R,6S)- or (5R,6R)-compounds, are favorable. With respect to the carbon atom at the 8-position, those having an R-configuration are preferred. With respect to the 4-position, the compounds wherein R_1 is an alkyl group

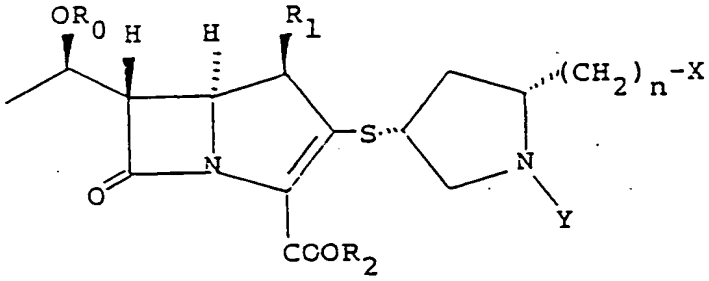
and which have an R-configuration, i.e. the (4R)-compounds, are favorable.

More preferred are the compounds (I) wherein R_1 is an alkyl group and which have a (4R,5S,6S,8R)-configuration, the compounds (I) wherein R_1 is a hydrogen atom and which have a (4R,5R,6S,8R)-configuration, etc.

The most preferred compounds include those of the formulas:



(I')



(I")

wherein R_0, R_1, R_2, X, Y, and n are each as defined above.

The isomers having the steric configurations as stated above can be prepared from the starting compounds (III) or (IV) having the corresponding configurations.

The starting compounds (III) can be prepared by various conventional methods. The compounds (III) wherein R_1 is a hydrogen atom are known per se in (1) Japanese Patent Publication (unexamined) No. 27169/80, (2)

J.Am.Chem.Soc., Vol. 103, 6765-6767 (1981), (3) J.Chem.Soc., Perkin I, 964-968 (1981), etc. and can be produced by the methods as described in said literatures (1) to (3). The compounds (III) wherein R_1 is a lower alkyl group are known per se in (4) Heterocycles, Vol. 21, 29-40 (1984), (5) EP-A-0071908, (6) EP-A-0126587, etc. and can be produced according to the methods as described in said literatures (4) to (6).

The starting mercaptan derivatives (IV) can be prepared from trans-4-hydroxy-L-proline or cis-4-hydroxy-D-proline by application of a series of per se conventional reactions thereto.

Of the carbapenem compounds (I), those wherein R_0 and R_2 are all hydrogen atoms exhibit an excellent antimicrobial activity against a wide variety of disease-causing bacteria including Gram-positive bacteria such as Staphylococcus aureaus, Staphylococcus epidermidis, Streptococcus pyrogenes and Streptococcus faecalis and Gram-negative bacteria such as Escherichia coli, Proteus mirabilis, Serratia marcescens and Psudomonas aeruginosa and are useful as antimicrobial agents. Further, these compounds are characteristic in exhibiting an excellent antimicrobial activity against beta-lactamase-producing strains.

Other compounds according to the invention are important intermediates for the synthesis of the carbapenem compounds having an antimicrobial activity.

The compounds according to the invention are also

characterized in general by their high physiochemical stability and excellent water solubility, although some variation is observed depending on the respective compounds.

Carbapenem compounds including thienamycin are known to have very poor stability in the human body, especially to dehydropeptidase (DHP-I) existing in a part of renal. The compounds of invention, particularly those represented by the formula (I) wherein R_1 is a (R)-methyl group, are also charactarized in general by their high stability to said enzyme DHP-I, although varying depending on the respective compounds. Some of the compounds of the invention have extremely high stability.

The compounds of the present invention can be used as antimicrobial agents for treating bacteria-caused infectious diseases in the form of oral preparations such as tablets, capsules, powders, syrups, etc. or non-oral preparations such as intravenous injections, intramuscular injections, rectal preparations, etc.

The dosage of the antimicrobial agent varies depending upon the symptoms, ages, bodyweight, dosage forms, times of doses and the like, but usually ranges from about 100 mg to 3,000 mg per day in a single dose or several divided doses for adults. The above dose level can be increased or decreased according to necessity.

The present invention will now be illustrated in greater detail with reference to the following Reference Examples and Examples, but it should be understood that these examples are given only for illustrative purposes and

are not limiting the present invention.

In Reference Examples and Examples, the following abbreviations are used:

PNZ: p-Nitrobenzyloxycarbonyl group

PMZ: p-Methoxybenzyloxycarbonyl group

PMB: p-Methoxybenzyl group

PNB: p-Nitrobenzyl group

Ph : Phenyl group

Ac : Acetyl group

Ms : Methanesulfonyl group

Ts : p-Toluenesulfonyl group

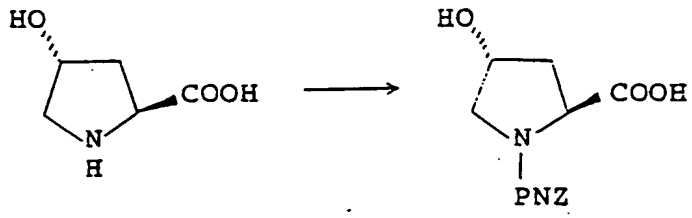
TBDMS: t-Butyldimethylsilyl group

tBu: t-Butyl group

Me : Methyl group

Et : Ethyl group

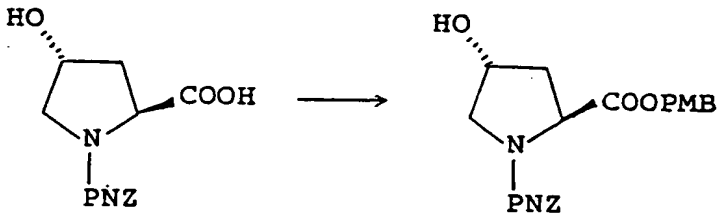
Reference Example 1



trans-4-Hydroxy-L-proline (6.55 g) and triethylamine (7.5 ml) were dissolved in 15 ml of water, and a solution of 15.95 g of S-p-nitrobenzyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine in 35 ml of dioxane was dropwise added thereto. The resulting mixture was stirred at room temperature for 1.5 hours and allowed to stand overnight. To the reaction mixture was added 30 ml of 2N sodium hydroxide solution under ice-cooling, and the resultant mixture was shaken with diethyl ether. The aqueous layer was separated from the ethereal layer, the ethereal layer was washed with 20 ml of 1N sodium hydroxide solution, and the washing was combined with the aqueous layer. The combined mixture was made acidic with 100 ml of 2N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract was washed with 2N hydrochloric acid, dried over anhydrous sodium sulfate and distilled to remove the solvent. The resulting crude crystals were washed with ethyl acetate to obtain trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline. M.P., 134.3 - 135.5°C

IR ν_{max}^{Nujol} cm^{-1}: 3300 (br), 1738, 1660, 1605, 1520, 1340, 1205, 1172, 1070, 965.

Reference Example 2

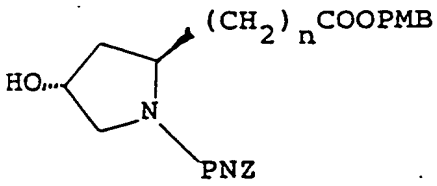


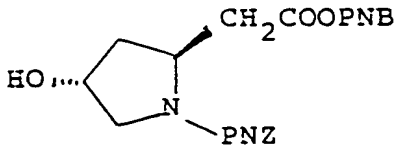
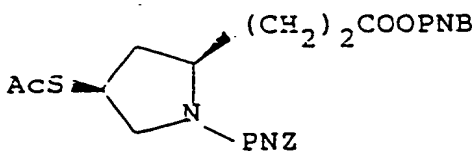
trans-1-(p-Nitrobenzyloxycarbonyl)-4-hydroxy-L-proline (15.0 g) and triethylamine (13.5 ml) were dissolved in 150 ml of dry dimethylformamide, and 12.66 ml of p-methoxybenzyl chloride was dropwise added thereto under nitrogen stream, followed by stirring at 70°C for 10 hours. The reaction mixture was diluted with 500 ml of ethyl acetate, washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. Recrystallization of the residue from diethyl ether gave trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline p-methoxybenzyl ester. M.P., 83 - 85°C.

IR ν_{max}^{film} cm^{-1}: 3430, 1735, 1705, 1510, 1340, 1245, 1160.

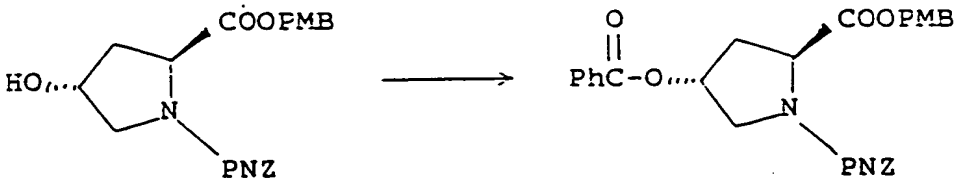
In the same procedure as described above but using the corresponding acid, the p-methoxybenzyl ester derivatives as shown in Table 1 were obtained.

Table 1



No.	n	Physical data
1	1	IR ν_{max}^{neat} cm^{-1}: 1695, 1606, 1518, 1400, 1360, 1240, 1107
2	2	IR ν_{max}^{neat} cm^{-1}: 1725, 1700, 1608, 1516, 1425, 1400, 1345
3	3	IR ν_{max}^{neat} cm^{-1}: 1720, 1688, 1515, 1400, 1343
4		IR ν_{max}^{neat} cm^{-1}: 1740, 1702, 1523, 1405, 1345
5		IR ν_{max}^{neat} cm^{-1}: 1732, 1697, 1515, 1393, 1342

Reference Example 3

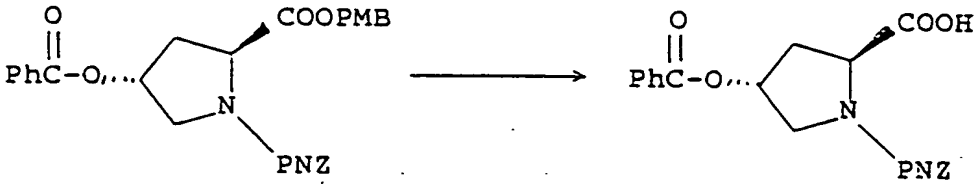


trans-1-(p-Nitrobenzyloxycarbonyl)-4-hydroxy-L-proline p-methoxybenzyl ester (49 g) was dissolved in 300

ml of dry tetrahydrofuran, and 33 ml of triethylamine, 9.59 g of 4-dimethylaminopyridine and 33.2 g of benzoyl chloride were added thereto, followed by stirring under reflux for 5 hours. The reaction mixture was cooled down to room temperature and distilled to remove the solvent. The residue was diluted with ethyl acetate, washed successively with water, dilute hydrochloric acid, water, a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to remove the solvent. Recrystallization of the residue from ethyl acetate gave trans-1-(p-nitrobenzyloxycarbonyl)-4-benzoyloxy-L-proline p-methoxybenzyl ester.

IR ν_{max}^{Nujol} cm^{-1}: 1740, 1716, 1703, 1608, 1516, 1343.

Reference Example 4



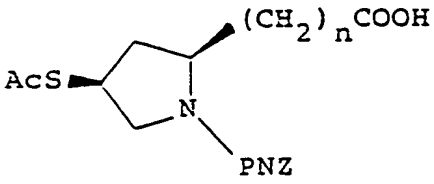
trans-1-(p-Nitrobenzyloxycarbonyl)-4-benzoyloxy-L-proline p-methoxybenzyl ester (61.3 g) and anisole (12.8 ml) were stirred together with 70 ml of trifluoroacetic acid at room temperature for 30 minutes. The reaction mixture was distilled to remove trifluoroacetic acid, and the residue was diluted with ethyl acetate and a saturated sodium bicarbonate solution. The precipitated crystals were separated by filtration and dissolved in methanol. The solution was acidified with 6N hydrochloric acid to pH 1.0,

diluted with ethyl acetate, washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation to give trans-1-(p-nitrobenzyloxycarbonyl)-4-benzoyloxy-L-proline.

IR $\overset{CHCl_3}{max}$ cm^{-1}: 1720, 1610, 1527, 1436, 1350, 1275, 1114.

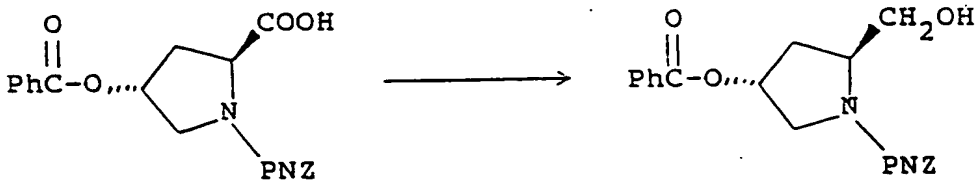
In the same procedure as described above but using the corresponding p-methoxybenzyl ester, the acid derivatives as shown in Table 2 were obtained.

Table 2



No.	n	Physical data
1	1	IR^{neat}_{max} cm^{-1}: 1690, 1602, 1517, 1400, 1342, 1108
2	2	IR^{neat}_{max} cm^{-1}: 1690, 1600, 1510, 1420, 1393, 1338
3	3	IR^{neat}_{max} cm^{-1}: 1703, 1528, 1410, 1350, 1110

Reference Example 5

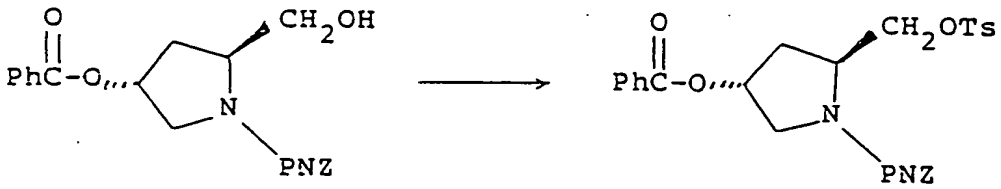


trans-1-(p-Nitrobenzyloxycarbonyl)-4-benzoyloxy-L-proline (43.1 g) was dissolved in 86 ml of dry tetrahydrofuran, and 12.2 g of triethylamine was added thereto.

Ethyl chloroformate (13.0 g) was dropwise added to the mixture at -10 to -15°C under nitrogen stream, followed by stirring for 15 minutes at the same temperature. The reaction mixture was separated by filtration, and the filtrate was added to a solution of 7.68 g of sodium borohydride in 78 ml of water at 0°C. After stirring for 1 hour at the same temperature, the reaction mixture was diluted with ethyl acetate and washed successively with water, dilute hydrochloric acid and water. A saturated sodium bicarbonate solution was added to the ethereal layer to precipitate crystals. The crystals were removed by filtration, and the filtrate was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation to give (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-hydroxymethyl-4-benzoyloxypyrrolidine.

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1530, 1435, 1352, 1280, 1115.

Reference Example 6

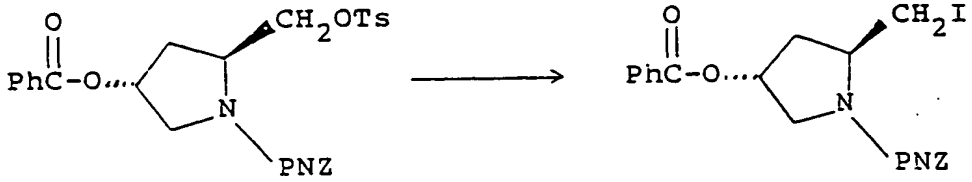


(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-hydroxymethyl-4-benzoyloxypyrrolidine (32.6 g) was dissolved in 64 ml of dry pyridine, and 28.02 g of p-toluenesulfonyl chloride was added thereto, followed by stirring at room temperature for 12 hours. The reaction mixture was diluted with water and extracted with a mixture of ethyl acetate and

dichloromethane (4:1). The extract was washed successively with brine, dilute hydrochloric acid, brine, a saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate and distilled to remove the solvent. Recrystallization of the residue from ethyl acetate gave (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-p-toluenesulfonyloxymethyl-4-benzoyloxypyrrolidine.

IR $\overset{CHCl_3}{max}$ cm^{-1}: 1700, 1518, 1342, 1265, 1172, 1090.

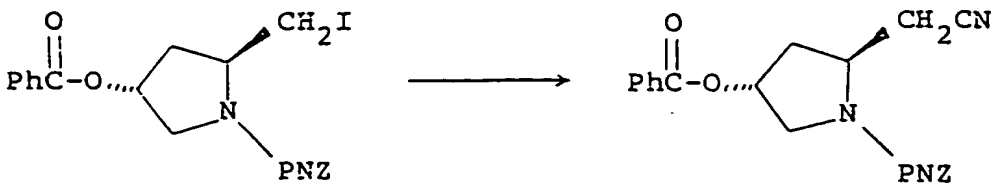
Reference Example 7



(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-p-toluenesulfonyloxymethyl-4-benzoyloxypyrrolidine (35.82 g) was dissolved in 90 ml of methylethylketone, and 19.29 g of sodium iodide was added thereto, followed by stirring under reflux for 1 hour. The reaction mixture was cooled down to room temperature and filtered. The filtrate was distilled to remove the solvent. The residue was diluted with ethyl acetate, washed successively with water, a sodium hypochlorite solution and water and dried over anhydrous sodium sulfate. The solvent was removed by distillation to give (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-iodomethyl-4-benzoyloxypyrrolidine.

IR $\overset{Nujol}{max}$ cm^{-1}: 1710, 1515, 1394, 1275, 1115.

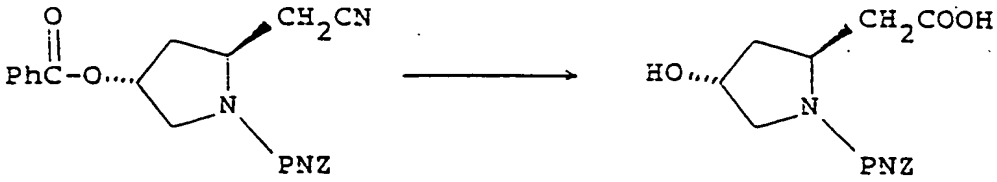
Reference Example 8



(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-iodomethyl-4-benzoyloxypyrrolidine (5.24 g) was dissolved in 26 ml of dry dimethylformamide, and 539 mg of sodium cyanide was added thereto, followed by stirring at room temperature for 24 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel column chromatography to give (2R,4R)-1-(p-nitrobenzyloxycarbonyl)-2-cyanomethyl-4-benzoyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 2250, 1715, 1605, 1520, 1400, 1345, 1275, 1110.

Reference Example 9

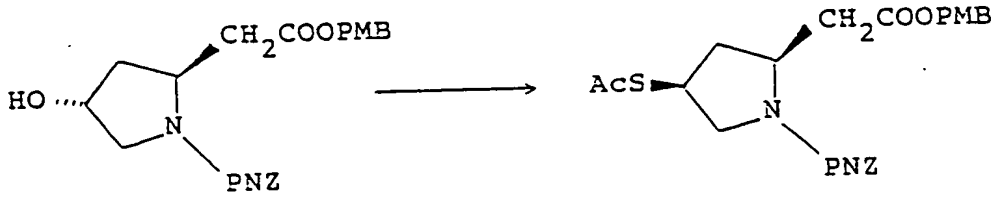


(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-cyanomethyl-4-benzoyloxypyrrolidine (3.0 g) was dissolved in 10 ml of acetic acid and 10 ml of conc. hydrochloric acid. After refluxing for 3 hours, the reaction mixture was cooled down to room temperature and distilled to remove the solvent. The residue was diluted with 4 ml of water and 25 ml of 1N sodium hydroxide solution. A solution of 1.53 g of

p-nitrobenzyl chloroformate in 6 ml of ethyl acetate and 2 ml of tetrahydrofuran was added to the above mixture at 0°C, followed by stirring at the same temperature for 30 minutes. The reaction mixture was separated. The aqueous layer was acidified with 6N hydrochloric acid to pH 1.0 and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation to give (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-carboxymethyl-4-hydroxypyrrolidine.

IR ν_{max}^{Nujol} cm^{-1}: 1690, 1603, 1517, 1460, 1200, 1116.

Reference Example 10



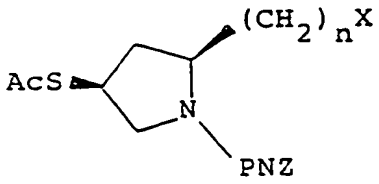
(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-p-methoxybenzyloxycarbonylmethyl-4-hydroxypyrrolidine (1.40 g) and triphenylphosphine (1.18 g) were dissolved in 7 ml of dry tetrahydrofuran under nitrogen stream. To the resulting solution was added 783 mg of diethyl azodicarboxylate at 0°C, followed by stirring at the same temperature for 30 minutes. Thereafter, 342 mg of thioacetic acid was added thereto, and the mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate, washed successively with a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica

gel column chromatography to give (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-p-methoxybenzyloxycarbonylmethyl-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1700, 1605, 1510, 1400 1343, 1240.

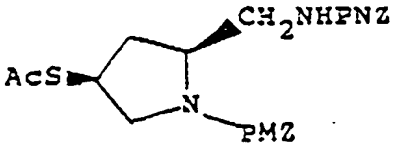
In the same procedure as above but using the corresponding alcohol, the thioacetate derivatives as shown in Table 3 were obtained.

Table 3

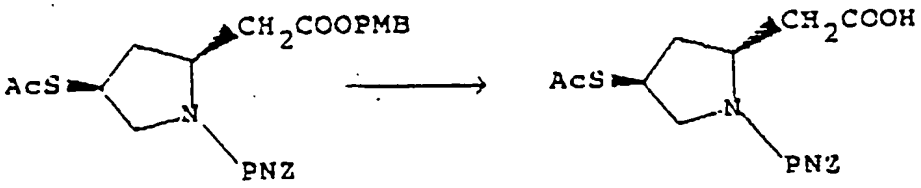


No.	X	n	Physical data
1	$NHCONH_2$	1	IR ν_{max}^{neat} cm^{-1}: 1703 (sh), 1685, 1520, 1400, 1340, 1110
2	$NHCONMe_2$	1	IR ν_{max}^{neat} cm^{-1}: 1685, 1635, 1520, 1400, 1342, 1115
3	NHCOOEt	1	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1710, 1505, 1340, 1230, 1055
4	NHAc	1	IR ν_{max}^{neat} cm^{-1}: 1690, 1510, 1395, 1340 1110, 845
5	OTBDMS	1	IR ν_{max}^{neat} cm^{-1}: 1710, 1525, 1400, 1345, 1253, 1115
6	COOPMB	2	IR ν_{max}^{neat} cm^{-1}: 1730, 1700, 1606, 1516 1398, 1344, 1242
7	SMe	1	IR ν_{max}^{neat} cm^{-1}: 1710, 1612, 1528, 1403, 1350, 1108

(Continued)

No.	X	n	Physical data
8	SO_2Me	1	IR ν_{max}^{Nujol} cm^{-1}: 1701, 1522, 1453, 1343, 1300, 1125
9	COOPMB	3	IR ν_{max}^{neat} cm^{-1}: 1732, 1708, 1518, 1345, 1243
10	COOtBu	4	IR ν_{max}^{neat} cm^{-1}: 1720 (sh), 1700, 1520, 1400, 1342
11	COOPNB	1	IR ν_{max}^{neat} cm^{-1}: 1740, 1700, 1525, 1403, 1343
12	$CH=NNMe_2$	1	IR ν_{max}^{neat} cm^{-1}: 1700, 1518, 1398, 1340
13	CH=N-OMe	1	IR ν_{max}^{neat} cm^{-1}: 1700, 1518, 1393, 1340
14	CN	1	IR ν_{max}^{neat} cm^{-1}: 2245, 1690, 1512, 1340
15	OAc	2	IR ν_{max}^{neat} cm^{-1}: 1740, 1705, 1520, 1400, 1345
16	OAc	3	IR ν_{max}^{neat} cm^{-1}: 1740, 1710, 1523, 1402, 1348
17			IR ν_{max}^{neat} cm^{-1}: 1725 (sh), 1686, 1515, 1407, 1342, 1242

Reference Example 11

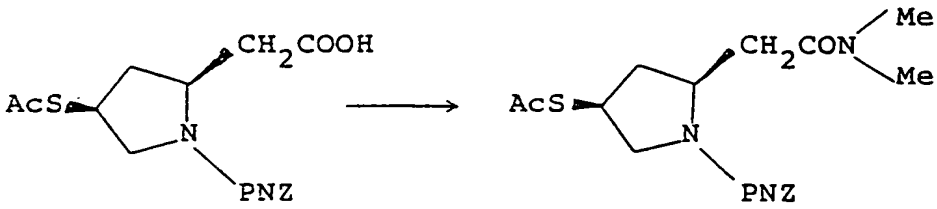


(2R,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-p-methoxybenzyloxycarbonylmethyl-4-acetylthiopyrrolidine (810 mg) and anisole (330 mg) were stirred together with 4 ml of trifluoroacetic acid at room temperature for 30 minutes.

The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel thin layer chromatography to obtain (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-carboxymethyl-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1690, 1602, 1517, 1400, 1342, 1108.

Reference Example 12

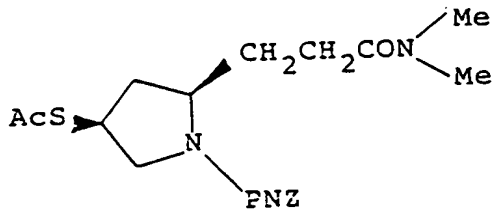


(2R,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-carboxymethyl-4-acetylthiopyrrolidine (125 mg) was dissolved in 1 ml of dry methylene chloride, and 0.1 ml of oxalyl chloride and a catalytic amount of dimethylformamide were added thereto, follwed by stirring at room temperature for 2 hours. The reaction mixture was distilled to remove the solvent, and dry benzene was added to the residue, followed by distillation of benzene. After two times repetition of the above procedure, the resulting residue was dissolved in 2 ml of dry methylene chloride. The resultant mixture was added to a solution of 45 mg of dimethylamine in 1.5 ml of dry methylene chloride and 0.2 ml of dry tetrahydrofuran under nitrogen stream at 0°C, followed by stirring at the same temperature for 30 minutes. The reaction mixture was diluted with methylene chloride, washed successively with water, dilute hydrochloric acid, water, a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue

was purified by silica gel thin layer chromatography to obtain (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylaminocarbonylmethyl-4-acetylthiopyrrolidine.

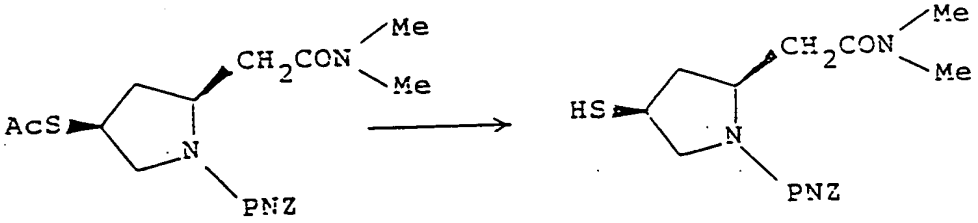
IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1700, 1635, 1518, 1398, 1342, 1100.

In the same procedure as above but using the corresponding acid, there was prepared (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-(2-dimethylaminocarbonylethyl)-4-acetylthiopyrrolidine of the formula:



IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1690, 1630, 1515, 1400, 1346, 1110.

Reference Example 13



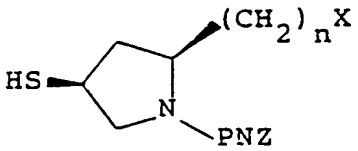
(2R,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-dimethylaminocarbonylmethyl-4-acetylthiopyrrolidine (100 mg) was dissolved in 3 ml of methanol, and 0.24 ml of 1N sodium hydroxide solution was added thereto under nitrogen stream at room temperature, followed by stirring at the same temperature for 15 minutes. 1N Hydrochloric acid (0.24 ml) was added thereto, followed by concentration under reduced pressure. The concentrate was diluted with methylene chloride, washed with water, dried over anhydrous sodium

sulfate and distilled to remove the solvent to obtain (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylamino-carbonylmethyl-4-mercaptopyrrolidine.

IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1700, 1640, 1520, 1400, 1345, 1100.

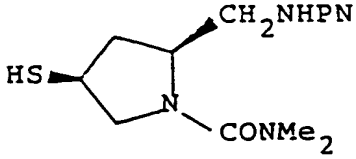
In the same procedure as above but using the corresponding thioacetate, the mercaptan derivatives as shown in Table 4 were obtained.

Table 4

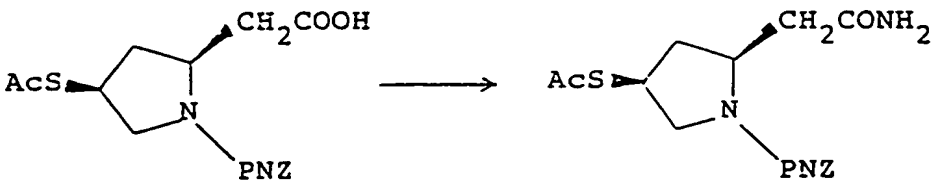


No.	X	n	Physical data
1	$CONH_2$	1	IR $\overset{CHCl_3}{\underset{max}{}}$ cm^{-1}: 1785, 1605, 1520, 1400, 1340, 1110
2	COOMe	1	IR $\overset{neat}{\underset{max}{}}$ cm^{-1}: 1750, 1695, 1510, 1400 1342, 1200, 1100
3	$NHCONH_2$	1	IR $\overset{neat}{\underset{max}{}}$ cm^{-1}: 1683, 1600, 1515, 1338, 1210, 1100
4	$NHCONMe_2$	1	IR $\overset{neat}{\underset{max}{}}$ cm^{-1}: 1690, 1630, 1520, 1398, 1340, 1110
5	NHCOOEt	1	IR $\overset{CHCl_3}{\underset{max}{}}$ cm^{-1}: 3430, 1710, 1510, 1400, 1340, 1210, 1055
6	NHA_c	1	IR $\overset{CHCl_3}{\underset{max}{}}$ cm^{-1}: 2440, 1680, 1515, 1395, 1340, 1185, 1105, 840
7	$OCONMe_2$	1	IR $\overset{neat}{\underset{max}{}}$ cm^{-1}: 1703, 1518, 1400, 1343, 1188, 1102
8	COOPNB	1	IR $\overset{neat}{\underset{max}{}}$ cm^{-1}: 1740, 1700, 1510, 1403 1345
9	OCONHMe	1	IR $\overset{neat}{\underset{max}{}}$ cm^{-1}: 1708, 1520, 1400, 1342, 1255, 1103
10	OAc	1	IR $\overset{neat}{\underset{max}{}}$ cm^{-1}: 1739, 1708, 1510, 1400

(Continued)

No.	X	n	Physical data
11	OCOOEt	1	IR ν_{max}^{neat} cm^{-1}: 1743, 1710, 1523, 1400, 1345, 1260
12	$CONH_2$	2	IR ν_{max}^{neat} cm^{-1}: 1680, 1600, 1510, 1395, 1340, 1200
13	CONHMe	2	IR ν_{max}^{Nujol} cm^{-1}: 1692, 1630, 1520, 1400, 1345
14	$CONMe_2$	2	IR ν_{max}^{neat} cm^{-1}: 1705, 1640, 1523, 1403, 1350, 1110
15	SMe	1	IR ν_{max}^{neat} cm^{-1}: 1705, 1605, 1522, 1404, 1348, 1103
16	SO_2Me	1	IR ν_{max}^{neat} cm^{-1}: 1700, 1604, 1526, 1398, 1340, 1299
17	OH	1	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685, 1608, 1520, 1403, 1303, 1105
18	OMe	1	IR ν_{max}^{neat} cm^{-1}: 1710, 1522, 1430, 1345, 1103
19	CONHMe	3	IR ν_{max}^{neat} cm^{-1}: 1702, 1650, 1520, 1405, 1348
20	CONHMe	4	IR ν_{max}^{neat} cm^{-1}: 1698, 1650, 1518, 1400, 1340
21	COOPNB	2	IR ν_{max}^{neat} cm^{-1}: 1730, 1700, 1508, 1400, 1340
22	$CONHNMe_2$	1	IR ν_{max}^{neat} cm^{-1}: 1700, 1522, 1400, 1348
23	CH=N-OMe	1	IR ν_{max}^{neat} cm^{-1}: 1700, 1520, 1400, 1343
24	CN	1	IR ν_{max}^{neat} cm^{-1}: 2240, 1690, 1512, 1333
25	$CH=NNMe_2$	1	IR ν_{max}^{neat} cm^{-1}: 1710, 1522, 1402, 1348
26			IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695, 1585, 1470, 1362, 1320

Reference Example 14

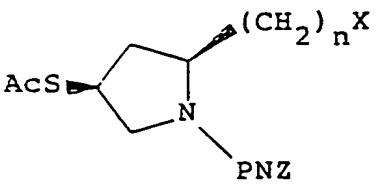


(2R,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-carboxymethyl-4-acetylthiopyrrolidine (82 mg) was dissolved in 1.5 ml of dry tetrahydrofuran, and 33 mg of triethylamine was added thereto. Ethyl chloroformate (35 mg) was added to the mixture under nitrogen stream at -10 to -15°C, followed by stirring at the same temperature for 30 minutes. 29 % (w/w) Aqueous ammonia (13 mg) was added at -40°C to the resulting mixture, followed by stirring at -30 to -40°C for 30 minutes. The reaction mixture was acidified with dilute hydrochloric acid, diluted with ethyl acetate, washed successively with water, a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-aminocarbonylmethyl-4-acetylthiopyrrolidine.

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705, 1603, 1518, 1395, 1342, 1260, 1105.

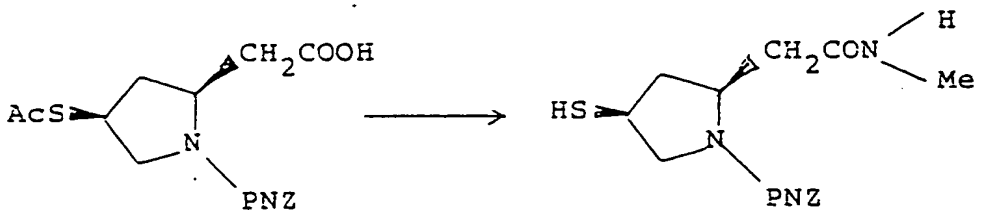
In the same procedure as above but using the corresponding acid, the amide derivatives as shown in Table 5 were obtained.

Table 5



No.	X	n	Physical data
1	$CONH_2$	2	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1683, 1602, 1518, 1398, 1340, 1110
2	CONHMe	2	IR ν_{max}^{neat} cm^{-1}: 1692, 1633, 1520, 1394, 1340, 1195
3	CONHMe	3	IR ν_{max}^{neat} cm^{-1}: 1695, 1645, 1518, 1400, 1340
4	CONHMe	4	IR ν_{max}^{neat} cm^{-1}: 1690, 1650, 1519, 1400, 1342

Reference Example 15(1)

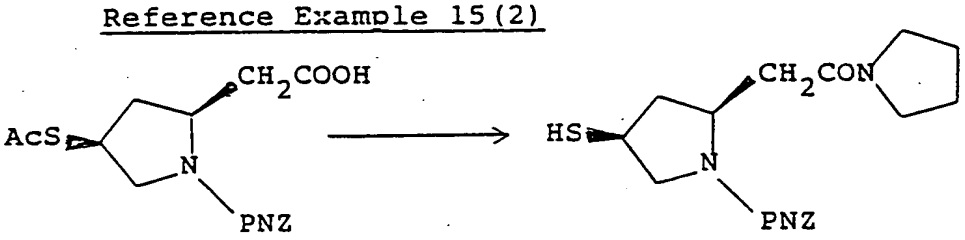


(2R,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-carboxymethyl-4-acetylthiopyrrolidine (153 mg) was dissolved in 2 ml of dry tetrahydrofuran, and 61 mg of triethylamine was added thereto. Ethyl chloroformate (65 mg) was added thereto at -10 to -15 °C under nitrogen stream, followed by stirring at the same temperature for 30 minutes. A 30 % ethanol solution of methylamine (414 mg) was added thereto at -40°C, and stirring was continued at -20 to -30°C for 1 hour. The reaction mixture was acidified with dilute hydrochloric acid, diluted with ethyl acetate, washed

successively with water, a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-methylaminocarbonylmethyl-4-mercaptopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1700, 1642, 1515, 1458, 1350.

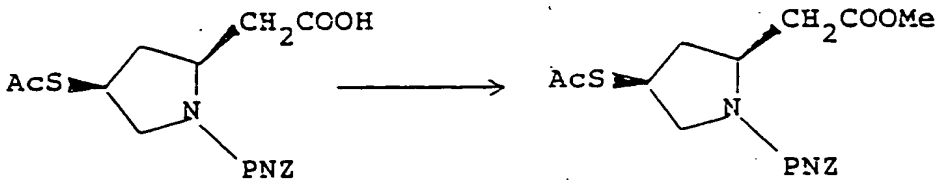
Reference Example 15(2)



Following the procedure as in Reference Example 15(1) but replacing methylamine by pyrrolidine, (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-pyrrolidinocarbonylmethyl-4-mercaptopyrrolidine was obtained.

IR ν_{max}^{neat} cm^{-1}: 1700, 1615, 1520, 1430, 1356, 1107.

Reference Example 16

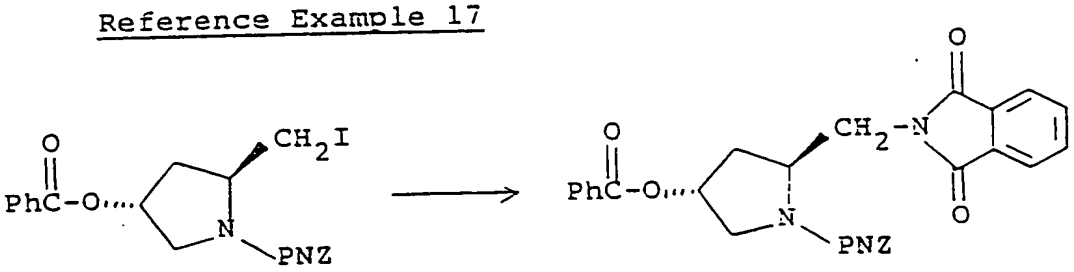


(2R,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-carboxymethyl-4-acetylthiopyrrolidine (148 mg) was dissolved in 2 ml of dry methylene chloride, and 0.2 ml of oxalyl chloride and a catalytic amount of dimethylformamide were added thereto, followed by stirring at room temperature for 2 hours. The reaction mixture was distilled to remove the solvent, and dry benzene was added thereto, followed by

distillation of benzene. After two times repetition of the above prodedure, the residue was dissolved in 2 ml of dry methylene chloride. The solution was added to a mixture of methanol (125 mg), triethylamine (81 mg) and dry methylene chloride (1 ml) under nitrogen stream with ice-cooling and stirred at the same temperature for 2 hours. The reaction mixture was washed successively with water and dilute hydrochloric acid, dried over anhydrous sodium sulfate and distilled to remove the solvent to obtain (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-methoxycarbonylmethyl-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1736, 1710, 1522, 1406, 1352, 1160.

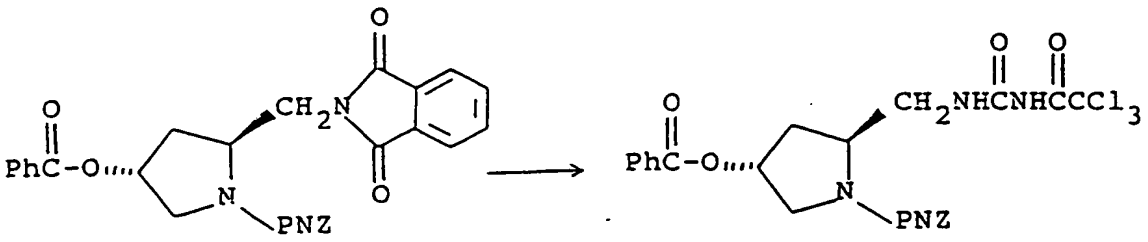
Reference Example 17



(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-iodomethyl-4-benzoyloxypyrrolidine (5.24 g) was dissolved in 21 ml of dry dimethylformamide, and 2.22 g of potassium phthalimide was added thereto, followed by stirring at 90°C for 6 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel column chromatography to obtain (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-phthalimidoylmethyl-4-benzoyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1775, 1720, 1605, 1522, 1346, 1275.

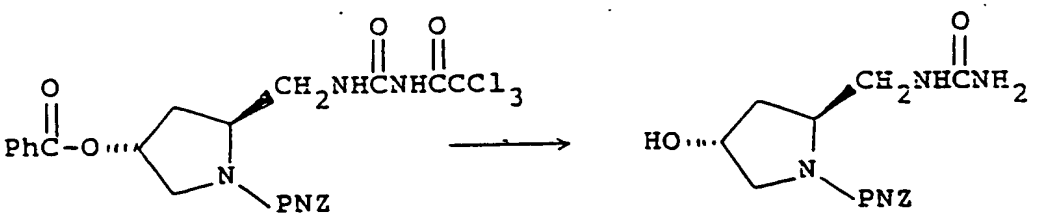
Reference Example 18



(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-phthalimidoylmethyl-4-benzoyloxypyrrolidine (490 mg) was dissolved in 20 ml of ethanol, and 432 mg of hydrazine hydrate was added thereto, followed by stirring under reflux for 30 minutes. The reaction mixture was cooled down to room temperature and filtered, and the filtrate was distilled to remove the solvent. The residue was dissolved in 3 ml of dry tetrahydrofuran, and 212 mg of trichloroacetyl isocyanate was added thereto, followed by stirring at room temperature for 3 hours. The resulting mixture was distilled off to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-trichloroacetylaminocarbonylaminomethyl-4-benzoyloxypyrrolidine.

IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1710, 1600, 1517, 1440, 1270, 1110.

Reference Example 19

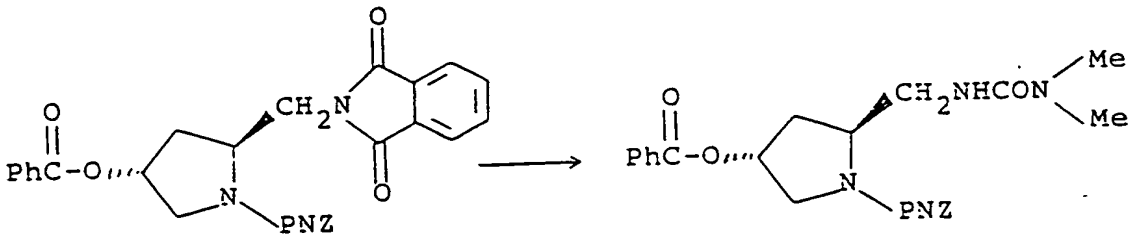


(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-trichloroacetylaminocarbonylaminomethyl-4-benzoyloxypyrrolidine (431

mg) was dissolved in 10 ml of methanol, and 1.48 ml of 1N sodium hydroxide solution was added thereto, followed by stirring at room temperature for 1.5 hours. 1N Hydrochloric acid (1.48 ml) was added thereto, followed by concentration to remove methanol. The residue was diluted with methylene chloride, washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-aminocarbonyl-aminomethyl-4-hydroxypyrrolidine.

IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1665, 1596, 1510, 1425, 1336, 1103.

Reference Example 20(1)

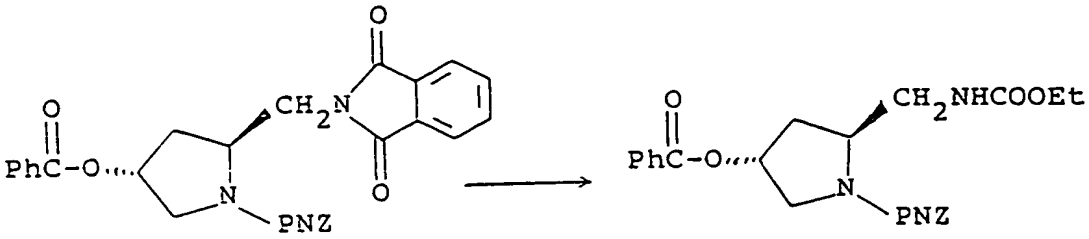


(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-phthal-imidoylmethyl-4-benzoyloxypyrrolidine (105 mg) and hydrazine hydrate (14 mg) were dissolved in 2 ml of ethanol. The resulting mixture was refluxed for 30 minutes. After removal of any insoluble material by filtration, the filtrate was distilled to remove the solvent. The residue was dissolved in 2 ml of tetrahydrofuran, and 115 mg of triethylamine and 107 mg of dimethylaminocarbonyl chloride were added thereto. The resulting mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate, washed successively with water, dilute hydrochloric acid,

water, a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel chromatography to obtain (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylaminocarbonylaminomethyl-4-benzoyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1710, 1640, 1530, 1345, 1275, 1110

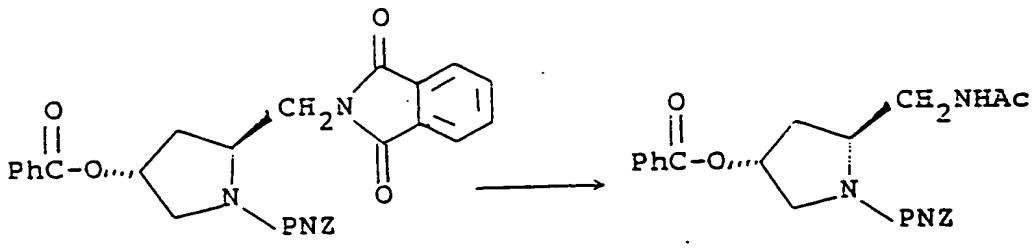
Reference Example 20(2)



Following the procedure as in Reference Example 20(1) but replacing dimethylaminocarbonyl chloride by ethyl chloroformate, (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-ethoxycarbonylaminoethyl-4-benzoyloxypyrrolidine was obtained.

IR ν_{max}^{neat} cm^{-1}: 1705, 1515, 1400, 1345, 1270, 1100.

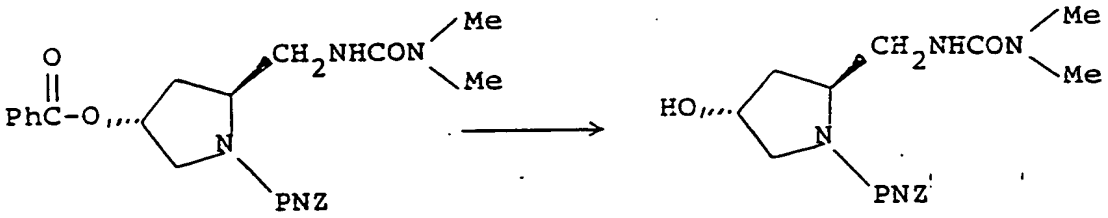
Reference Example 20(3)



Following the procedure as in Reference Example 20(1) but replacing dimethylaminocarbonyl chloride by acetyl chloride, (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-acetylaminomethyl-4-benzoyloxypyrrolidine was obtained.

IR ν_{max}^{neat} cm^{-1}: 1705, 1520, 1400, 1345, 1275, 1110.

Reference Example 21

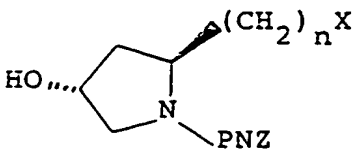


(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-dimethylaminocarbonylaminomethyl-4-benzoyloxyprrolidine (145 mg) was dissolved in methanol (2.4 ml), and 0.32 ml of 1N sodium hydroxide solution was added thereto. The resulting mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added 0.32 ml of 1N hydrochloric acid, and the mixture was distilled to remove methanol. The residue was diluted with methylene chloride, washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel chromatography to obtain (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylaminocarbonylaminomethyl-4-hydroxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1690, 1632, 1530, 1410, 1345, 1110.

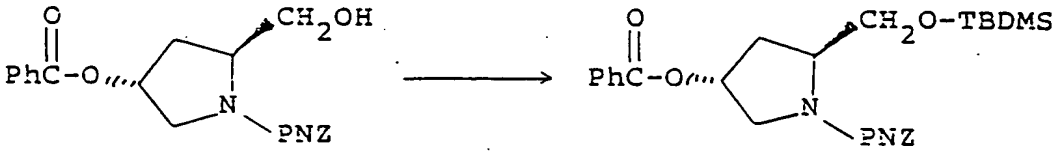
In the same procedure as above but using the corresponding benzoate, the following alcohol derivatives as shown in Table 6 were obtained.

Table 6



No.	X	n	Physical data
1	NHCOOEt	1	IR ν_{max}^{neat} cm^{-1}: 1690, 1530, 1410, 1350, 1260
2	NHAc	1	IR ν_{max}^{neat} cm^{-1}: 1685, 1520, 1425, 1345, 1185, 1110
3	OTBDMS	1	IR ν_{max}^{neat} cm^{-1}: 1700, 1525, 1430, 1343, 1108, 834
4	I	1	IR ν_{max}^{neat} cm^{-1}: 1690, 1610, 1520, 1435, 1404, 1350
5	SMe	1	IR ν_{max}^{neat} cm^{-1}: 1683, 1603, 1518, 1425, 1400, 1342
6	SO_2Me	1	IR ν_{max}^{neat} cm^{-1}: 1698, 1522, 1403, 1342, 1302, 1120
7	CN	1	IR ν_{max}^{neat} cm^{-1}: 2235, 1690, 1512, 1333

Reference Example 22

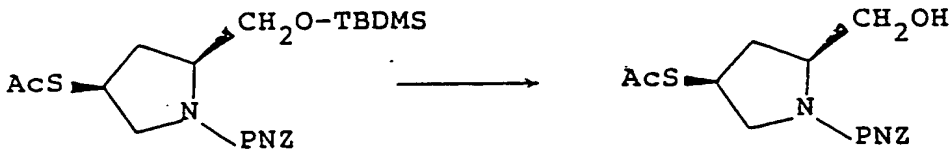


(2S,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-hydroxymethyl-4-benzoyloxypyrrolidine (1.09 g), imidazole (0.46 g) and t-butyldimethylsilyl chloride (0.49 g) were dissolved in 16.5 ml of dry dimethylformamide. The resulting mixture was stirred at room temperature for 2 hours, diluted with ethyl acetate, washed with water, dried over anhydrous magensium sulfate and distilled to remove the solvent. The residue was purified by silica gel chromatography to obtain

(2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-t-butyldimethylsilyloxymethyl-4-benzoyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1710, 1520, 1400, 1340, 1265, 1108.

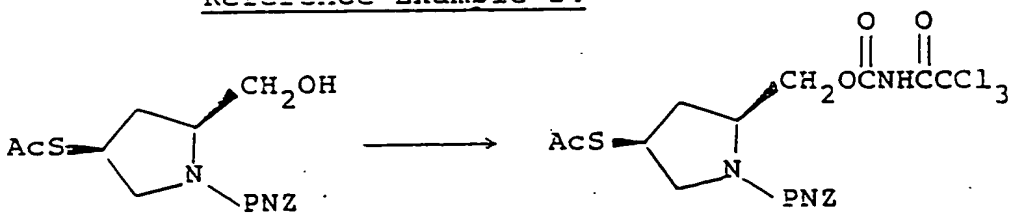
Reference Example 23



(2S,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-t-butyldimethylsilyloxymethyl-4-acetylthiopyrrolidine (0.85 g) was dissolved in methanol (8.5 ml), and 0.85 ml of 6N hydrochloric acid was added thereto. The resulting mixture was stirred at room temperature for 2.5 hours, diluted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate and distilled to remove the solvent. Recrystallization of the residue from diethyl ether gave (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-hydroxymethyl-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1695, 1520, 1430, 1402, 1343, 1110.

Reference Example 24

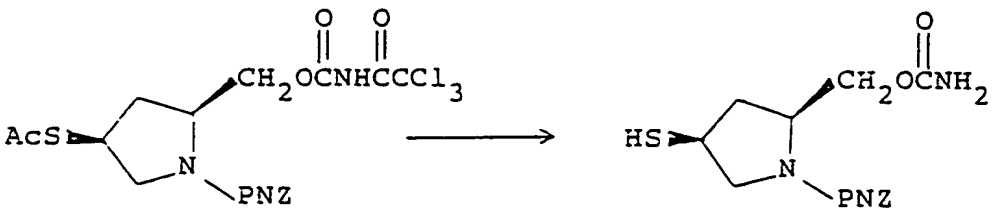


(2S,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-hydroxymethyl-4-acetylthiopyrrolidine (100 mg) was dissolved in 3 ml of dry ethyl acetate. To the solution was added 0.05 ml of trichloroacetyl isocyanate under ice-cooling in a nitrogen stream, followed by stirring at the same temper-

ature for 1 hour. The mixture was diluted with ethyl acetate, washed successively with a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-trichloroacetylaminocarbonyloxymethyl-4-acetylthiopyrrolidine.

IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1722, 1680, 1602, 1400, 1335, 1250, 1102.

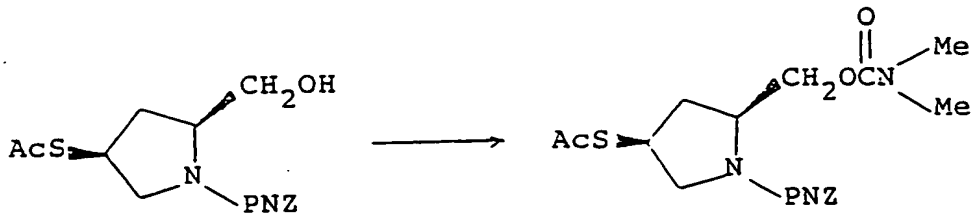
Reference Example 25



(2S,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-trichloroacetylaminocarbonyloxymethyl-4-acetylthiopyrrolidine (121 mg) was dissolved in 5.8 ml of methanol. To the solution was added 0.45 ml of 1N sodium hydroxide solution under ice-cooling in a nitrogen stream, followed by stirring at the same temperature for 40 minutes. After neutralization by 1.45 ml of 1N hydrochloric acid, the mixture was distilled to remove methanol. The residue was diluted with methylene chloride, washed with water, dried over anhydrous sodium sulfate and distilled to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-aminocarbonyloxymethyl-4-mercaptopyrrolidine.

IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1715, 1603, 1512, 1398, 1360, 1098.-

Reference Example 26

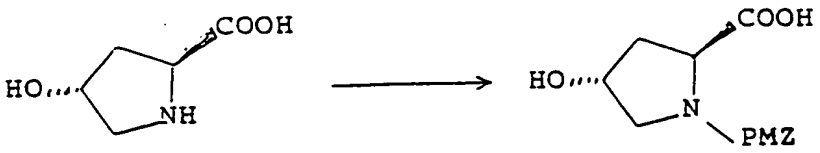


(2S,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-hydroxymethyl-4-acetylthiopyrrolidine (78 mg) was dissolved in 1 ml of dry pyridine, and 135 mg of 4-N,N-dimethylaminopyridine and 119 mg of dimethylaminocarbonyl chloride were added successively thereto, followed by stirring at 90 to 100°C for 20 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed successively with water, dilute hydrochloric acid, water, a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylaminocarbonyloxymethyl-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1700, 1515, 1393, 1340, 1185, 1100.

NMR δ ($CDCl_3$): 2.34 (3H,s), 2.89 (6H,s), 5.23 (2H,s).

Reference Example 27

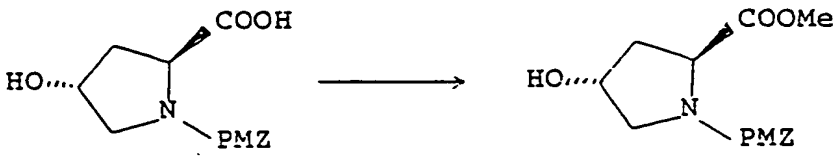


trans-4-Hydroxy-L-proline (13.1 g) and triethylamine (21 ml) were dissolved in 55 ml of water, and a solution of 33.44 g of S-p-methoxybenzyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine in 55 ml of dimethylformamide

was added thereto. The resulting mixture was stirred at room temperature for 12 hours, diluted with water and washed with ethyl acetate. The aqueous layer was acidified with 5N hydrochloric acid (pH 2) under ice-cooling and extracted with ethyl acetate. The extract was washed successively with dilute hydrochloric acid and brine, dried over anhydrous sodium sulfate and distilled to obtain trans-1-(p-methoxybenzyloxycarbonyl)-4-hydroxy-L-proline.

IR ν_{max}^{neat} cm^{-1}: 1670, 1435, 1350, 1240, 1168.

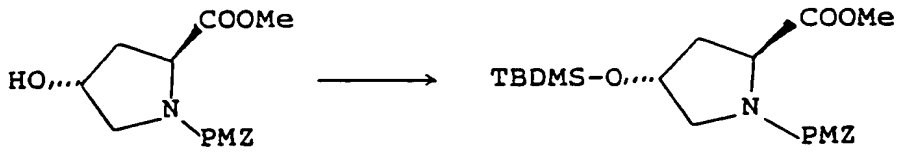
Reference Example 28



trans-1-(p-Methoxybenzyloxycarbonyl)-4-hydroxy-L-proline (5.0 g) was dissolved in 50 ml of methanol and 50 ml of tetrahydrofuran. An ethereal solution of diazomethane was added thereto under ice-cooling until nitrogen gas evolution stopped. The mixture was allowed to stand overnight and distilled to obtain trans-1-(p-methoxy-benzyloxy-carbonyl)-4-hydroxy-L-proline methyl ester.

IR ν_{max}^{neat} cm^{-1}: 1748, 1695, 1518, 1438, 1360, 1250, 1175.

Reference Example 29



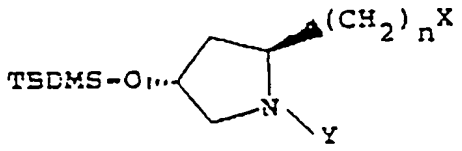
trans-1-(p-Methoxybenzyloxycarbonyl)-4-hydroxy-L-proline methyl ester (5.18 g), 3.79 g of triethylamine and

3.77 g of t-butyldimethylsilyl chloride were dissolved in 52 ml of dry dimethylformamide. The resulting mixture was stirred at room temperature for 3 hours, diluted with water, extracted with ethyl acetate, washed successively with water, dilute hydrochloric acid and water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel chromatography to obtain trans-1-(p-methoxybenzyloxycarbonyl)-4-t-butyldimethylsilyloxy-L-proline methyl ester.

IR ν_{max}^{neat} cm^{-1}: 1750, 1710, 1517, 1415, 1355, 1250, 1115.

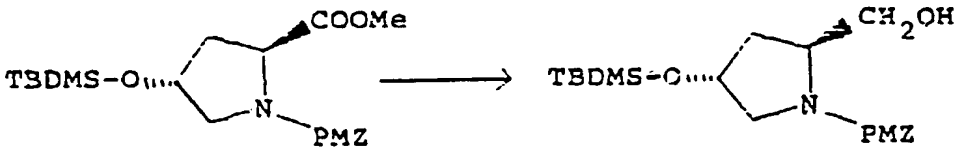
In the same procedure as above but using the corresponding alcohols, the t-butyldimethylsilyl ether derivatives as shown in Table 7 were obtained.

Table 7



No.	X	Y	n	Physical data
1	I	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1690, 1505, 1345, 1130 1100, 830
2	COOMe	Z	0	IR ν_{max}^{neat} cm^{-1}: 1750, 1710, 1410, 1350, 1250
3	COOMe	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1740, 1713, 1523, 1400, 1345
4	COOMe	PNZ	2	IR ν_{max}^{neat} cm^{-1}: 1738, 1705, 1523, 1405, 1350

Reference Example 30

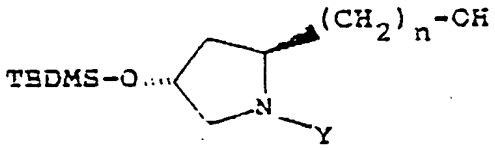


trans-1-(p-Methoxybenzyloxycarbonyl)-4-t-butyldimethylsilyloxy-L-proline methyl ester (5.64 g) was dissolved in 56.4 ml of dry tetrahydrofuran. Sodium borohydride (1.01 g) and lithium iodide (3.52 g) were added thereto. The resulting mixture was refluxed for 1 hour, diluted with water, extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and distilled off to obtain (2S,4R)-1-(p-methoxybenzyloxycarbonyl)-2-hydroxymethyl-4-t-butyldimethylsilyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1670, 1504, 1420, 1405, 1240, 1100.

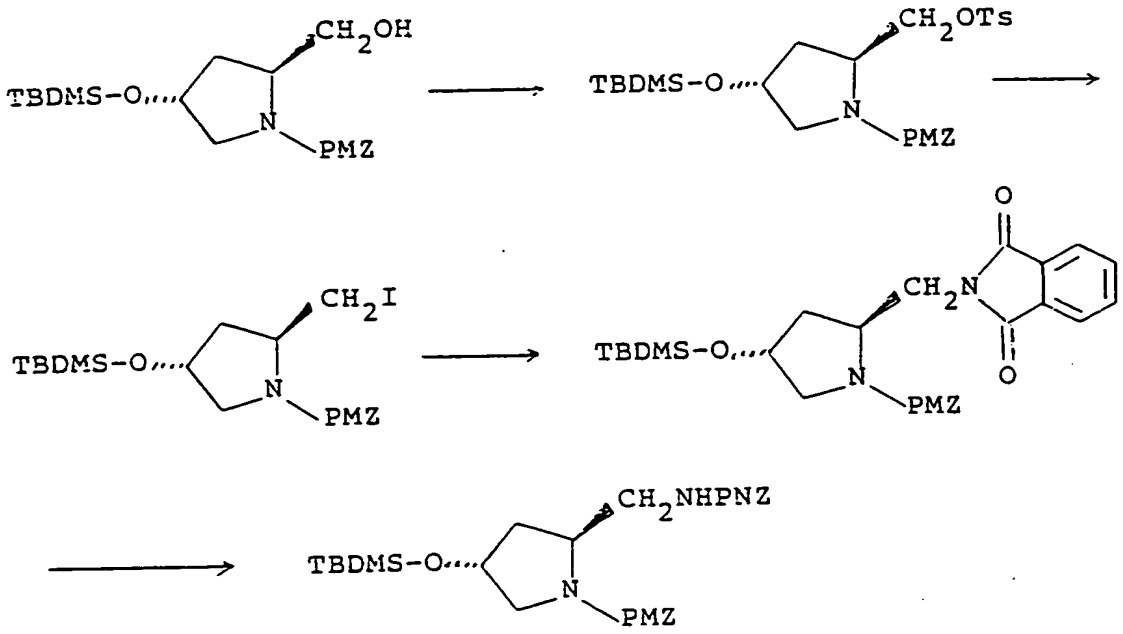
In the same procedure as above but using the corresponding methyl ester, the alchohol derivatives as shown in Table 8 were obtained.

Table 8



No.	n	Y	Physical data
1	1	Z	IR ν_{max}^{neat} cm^{-1}: 1700, 1415, 1355, 1250, 1110
2	3	Z	IR ν_{max}^{neat} cm^{-1}: 1702, 1410, 1358, 1258, 1118
3	2	PNZ	IR ν_{max}^{Nujol} cm^{-1}: 1678, 1522, 1463, 1402, 1345
4	3	PNZ	IR ν_{max}^{neat} cm^{-1}: 1690, 1525, 1405, 1350

Reference Example 31



Following the procedure as in Reference Examples 6, 7, 17 and 20(1), (2S,4R)-1-(p-methoxybenzyloxycarbonyl)-2-(p-nitrobenzyloxycarbonyl)aminomethyl-4-t-butyldimethylsilyloxypyrrolidine was obtained from the starting material, i.e., (2S,4R)-1-(p-methoxybenzyloxycarbonyl)-2-hydroxymethyl-4-t-butyldimethylsilyloxypyrrolidine.

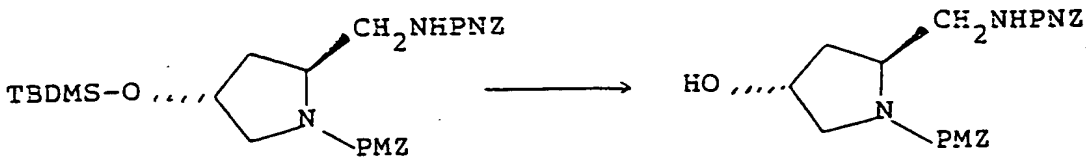
IR ν_{max}^{neat} cm^{-1}: 1720, 1690(sh), 1517, 1345, 1245, 1112.

Compound A: IR ν_{max}^{neat} cm^{-1}: 1700, 1505, 1402, 1354, 1240, 1166.

Compound B: IR ν_{max}^{neat} cm^{-1}: 1700, 1512, 1405, 1353, 1248, 1100.

Compound C: IR ν_{max}^{neat} cm^{-1}: 1757, 1715, 1510, 1390, 1245, 1111.

Reference Example 32

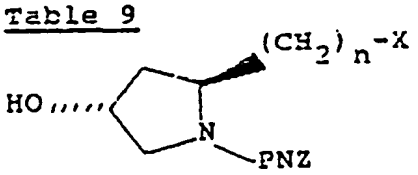


(2S,4R)-1-(p-Methoxybenzyloxycarbonyl)-2-(p-nitrobenzyloxycarbonyl)aminomethyl-4-t-butyldimethylsilyloxyprrolidine (850 mg) was dissolved in 8.5 ml of methanol and 1 ml of 6N hydrochloric acid was added thereto. The resulting mixture was stirred at room temperature for 30 minutes, diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel chromatography to obtain (2S,4R)-1-(p-methoxybenzyloxycarbonyl)-2-(p-nitrobenzyloxycarbonyl)aminomethyl-4-hydroxypyrrolidine.

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (sh), 1680, 1510, 1410, 1342, 1225.

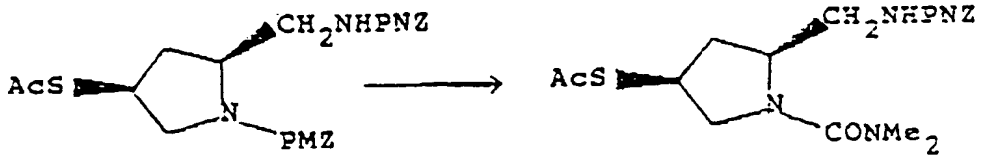
In the same procedure as above but using the corresponding t-butyldimethylsilyl ether, the alcohol derivatives as shown in Table 9 were obtained.

Table 9



No.	X	n	Physical data
1	COOtBu	4	IR ν_{max}^{neat} cm^{-1}: 1723 (sh), 1700, 1522, 1402, 1345
2	$CH=NNMe_2$	1	IR ν_{max}^{neat} cm^{-1}: 1700, 1520, 1400, 1343
3	CH=N-OMe	1	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1520, 1405, 1350
4	OAc	2	IR ν_{max}^{neat} cm^{-1}: 1740, 1700, 1525, 1415, 1355
5	OAc	3	IR ν_{max}^{neat} cm^{-1}: 1740, 1700, 1525, 1410, 1355

Reference Example 33

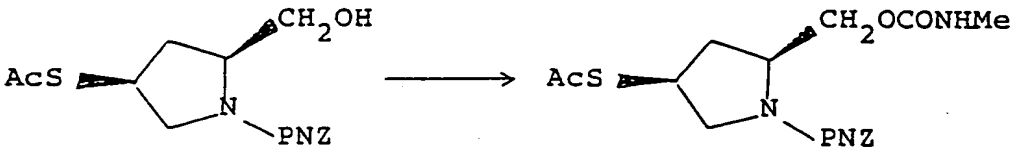


(2S,4S)-1-(p-Methoxybenzyloxycarbonyl)-2-(p-nitrobenzyloxycarbonyl)aminomethyl-4-acetylthio-pyrrolidine (500 mg), 216 mg of anisole and 4 ml of trifluoroacetic acid were stirred at room temperature for 1 hour. The mixture was distilled to remove the solvent. The residue was dissolved in dichloromethane, washed successively with a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was dissolved in 4 ml of tetrahydrofuran, and 152 mg of triethylamine and 141 mg of dimethylaminocarbonyl chloride were added thereto. The resulting mixture was stirred at room temperature for 30 minutes, diluted with ethyl acetate, washed successively with water, dilute hydrochloric acid, water, a saturated sodium bi-

carbonate solution and water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel chromatography to obtain (2S,4S)-1-dimethylaminocarbonyl-2-(p-nitrobenzyloxycarbonyl)aminomethyl-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1720, 1695 (sh), 1620, 1510, 1446, 1240.

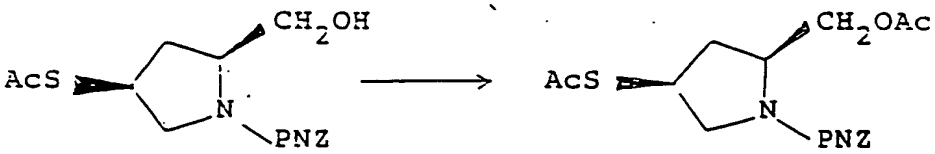
Reference Example 34(1)



(2S,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-hydroxymethyl-4-acetylthiopyrrolidine (200 mg) was dissolved in 2 ml of dry tetrahydrofuran. Methyl isocyanate (0.168 ml) was added thereto. The mixture was refluxed for 10 hours and distilled to remove the solvent. The residue was purified by silica gel chromatography to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-methylaminocarbonyloxymethyl-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1702, 1521, 1402, 1350, 1258, 1110.

Reference Example 34(2)

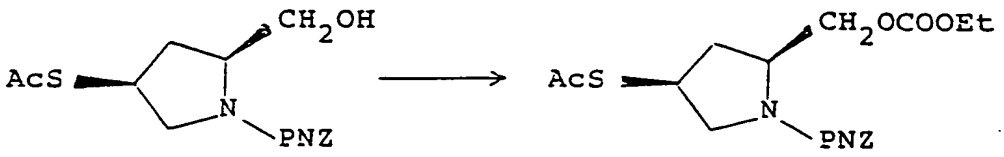


(2S,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-hydroxymethyl-4-acetylthiopyrrolidine (300 mg) was dissolved in 1.5 ml of dry pyridine. Acetic anhydride (1.5 ml) was added thereto. The resulting mixture was stirred at room temper-

ature for 5 hours, diluted with water, extracted with ether, washed successively with brine, dilute hydrochloric acid, brine, a saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate and distilled to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-acetoxymethyl-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1735, 1690, 1512, 1390, 1340, 1225.

Reference Example 34(3)



(2S,4S)-1-(p-Nitrobenzyloxycarbonyl)-2-hydroxymethyl-4-acetylthiopyrrolidine (177 mg), 76 mg of triethylamine and 61 mg of 4-N,N-dimethylaminopyridine were dissolved in 2 ml of dry dichloromethane. Ethyl chloroformate (81 mg) was added thereto under ice-cooling in a nitrogen stream. The mixture was stirred under ice-cooling for 3.5 hours, washed successively with water, dilute hydrochloric acid, water, a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and distilled to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-ethoxycarbonyloxymethyl-4-acetylthiopyrrolidine.

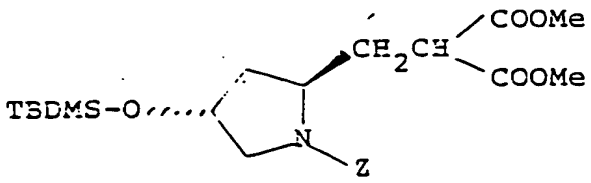
IR ν_{max}^{neat} cm^{-1}: 1740, 1702, 1520, 1400, 1343, 1248

Reference Example 35

Dimethyl malonate (660 mg) and 180 mg of 50 % sodium hydride in 12.5 ml of dry dimethylformamide were stirred at room temperature in a nitrogen stream for 15 minutes, and 1.34 g of (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-iodomethyl-4-t-butyldimethylsilyloxypyrrolidine was added thereto. The resulting mixture was stirred at room temperature for 15 hours, neutralized with 3.75 ml of 1N hydrochloric acid, diluted with water, extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel chromatogrphy to obtain (2R,4R)-1-(p-nitrobenzyloxycarbonyl)-2-(2,2-dimethoxycarbonylethyl)-4-t-butyldimethylsilyloxypyrrolidine.

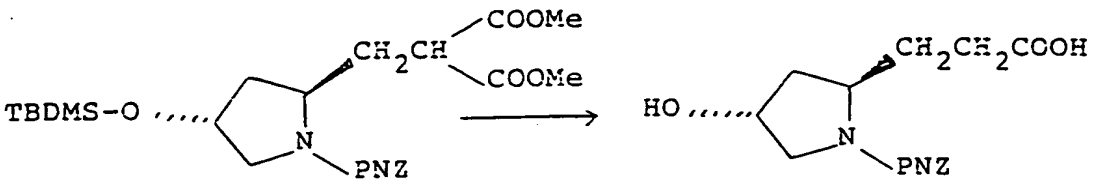
IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1755, 1710, 1527, 1400, 1350, 1258.

The following compound was obtained in the same procedure as above.



IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1735, 1700, 1430, 1403, 1342.

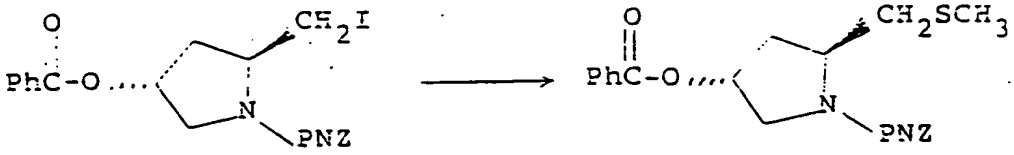
Reference Example 36



(2R,4R)-1-(p-Nitrobenzyloxycarbonyl)-2-(2,2-dimethoxycarbonylethyl)-4-t-butyldimethylsilyloxypyrrolidine (1.04 g) was dissolved in 6 ml of methanol, 3 ml of 4N sodium hydroxide solution was added thereto, and the resulting mixture was stirred at room temperature for 1.5 hours. The reaction mixture was acidified with 6 ml of 6N hydrochloric acid, and 5 ml of tetrahydrofuran was added thereto. The resulting mixture was stirred at room temperature for 2 days, diluted with water, adjusted to alkaline with a saturated sodium bicarbonate solution and extracted with ether. The aqueous layer was acidified (pH 1) with dilute hydrochloric acid, extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and distilled to obtain (2R,4R)-1-(p-nitrobenzyloxycarbonyl)-2-(2-carboxyethyl)-4-hydroxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1710, 1610, 1524, 1435, 1410, 1352.

Reference Example 37

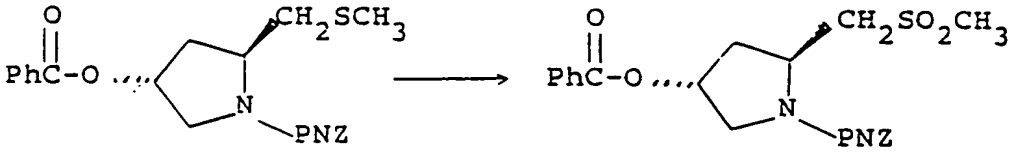


(2S,4R)-1-p-Nitrobenzyloxycarbonyl-2-iodomethyl-4-benzoyloxypyrrolidine (1.05 g) was dissolved in 10 ml of

dimethylformamide, and a solution of 1.40 g of 15 % methylmercaptan sodium salt in water was added thereto, followed by stirring at room temparature for 30 minutes under a nitrogen stream. The reaction mixture was diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2S,4R)-1-p-nitrobenzyloxycarbonyl-2-methylthiomethyl-4-benzoyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1700, 1597, 1518, 1392, 1339, 1263.

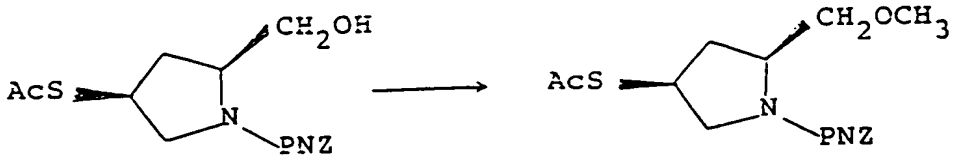
Reference Example 38



(2S,4R)-1-p-Nitrobenzyloxycarbonyl-2-methylthiomethyl-4-benzoyloxypyrrolidine (330 mg) was dissolved in 3.3 ml of dry chloroform, and 385 mg of m-chloroperbenzoic acid was added thereto, followed by refluxing for 6 hours. To the reaction mixture was added ether, and the resulting mixture was washed successively with a saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2S,4R)-1-p-nitrobenzyloxycarbonyl-2-methylsulfonylmethyl-4-benzoyloxypyrrolidine.

IR ν_{max}^{Nujol} cm^{-1}: 1719, 1692, 1518, 1450, 1345, 1299.

Reference Example 39



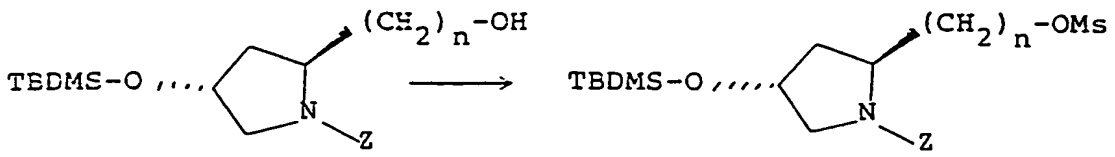
(2S,4S)-1-p-Nitrobenzyloxycarbonyl-2-hydroxymethyl-4-acetylthiopyrrolidine (354 mg) was dissolved in 30 ml of dichloromethane, and a solution of diazomethane in ether and a catalytic amount of BF_3-Et_2O complex were added thereto under ice-cooling, followed by stirring at the same temparature for 5 minutes. The reaction mixture was washed with brine, and after removal of any insoluble material by filtration from the dichloromethane layer, the filtrate was washed successively with a saturated sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate and distilled to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-methoxymethyl-4-acethylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1700, 1685, 1516, 1392, 1340, 1100.

Reference Example 40

The mesylate derivatives as shown in Table 10 were obtained from the corresponding alcohols in the same procedure as in Reference Example 6 but replacing p-toluenesulfonyl chloride by methanesulfonyl chloride.

Table 10

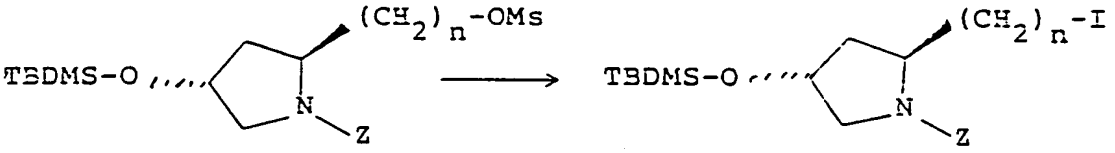


No.	n	Physical data
1	1	IR ν_{max}^{neat} cm^{-1}: 1700, 1410, 1350, 1250, 1172
2	3	IR ν_{max}^{neat} cm^{-1}: 1698, 1410, 1352, 1250, 1175

Reference Example 41

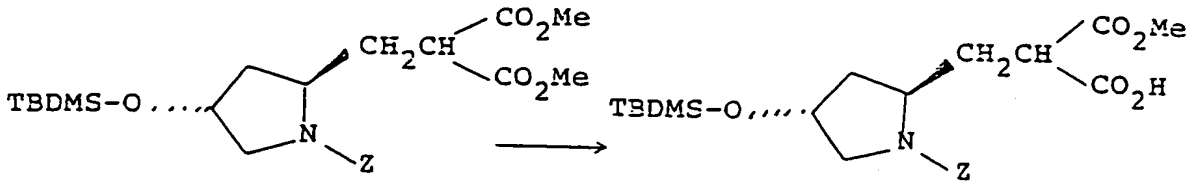
The iodide derivatives as shown in Table 11 were obtained from the corresponding mesylates in the same procedure as in Reference Example 7.

Table 11



No.	n	Physical data
1	1	IR ν_{max}^{neat} cm^{-1}: 1700, 1403, 1353, 1250, 1103
2	3	IR ν_{max}^{neat} cm^{-1}: 1700, 1405, 1352, 1250, 1102

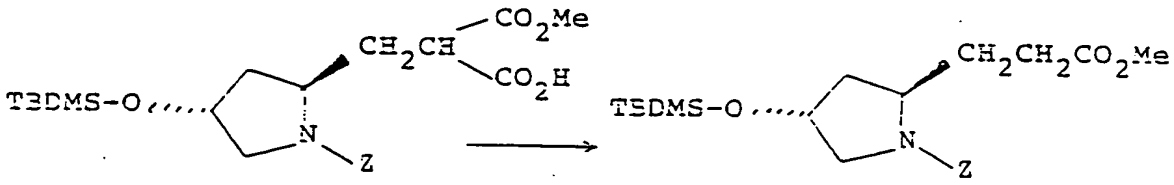
Reference Example 42



(2R,4R)-1-Benzyloxycarbonyl-2-(2,2-dimethoxycarbonyl)ethyl-4-t-butyldimethylsilyloxypyrrolidine (18 g) was dissolved in 180 ml of methanol, and 36 ml of 1N sodium hydroxide solution was added thereto, followed by stirring at room temparature for 18 hours. To the reaction mixture was added 36 ml of 1N hydrochloric acid, and the resulting mixture was distilled to remove the solvent. The residue was diluted with ethyl acetate, dried over anhydrous sodium sulfate and distilled to obtain (2R,4R)-1-benzyloxycarbonyl-2-(2-carboxy-2-methoxylcarbonyl)ethyl-4-t-butyldimethylsilyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1732, 1710, 1680, 1420, 1350.

Reference Example 43

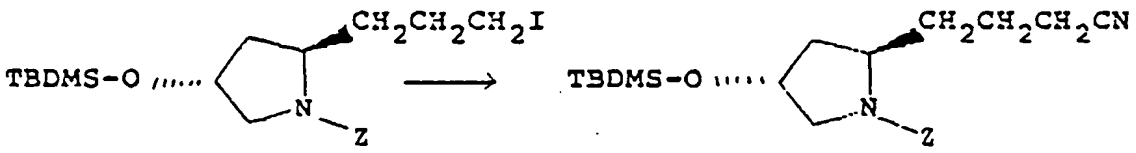


(2R,4R)-1-Benzyloxycarbonyl-2-(2-carboxy-2-methoxycarbonyl)ethyl-4-t-butyldimethylsilyloxypyrrolidine (18 g) was dissolved in 90 ml of dry dimethylsulfoxide, followed by stirring at 140°C for 3 hours. The reaction mixture was poured into ice-water, extracted with ethyl acetate, dried over anhydrous sodium sulfate and distilled to obtain (2R,4R)-1-benzyloxycarbonyl-2-(2-methoxycarbonyl)-

ethyl-4-t-butyldimethylsilyloxypyrrolidine.

IR $\overset{neat}{max}$ cm^{-1}: 1740, 1705, 1410, 1358, 1258.

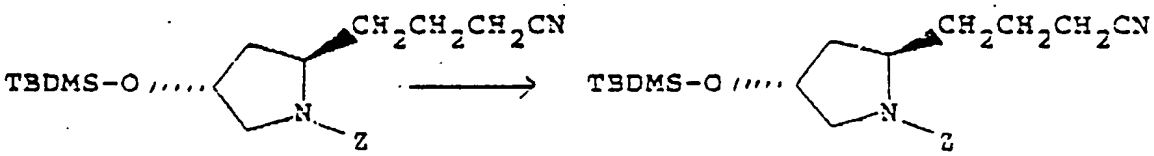
Reference Example 44



Following the procedure as in Reference Example 8 but using (2R,4R)-1-benzyloxycarbonyl-2-(3-iodopropyl)-4-t-butyldimethylsilyloxypyrrolidine as the starting material, (2R,4R)-1-benzyloxycarbonyl-2-(3-cyanopropyl)-4-t-butyldimethylsilyloxypyrrolidine was obtained.

IR $\overset{neat}{max}$ cm^{-1}: 2250, 1705, 1415, 1358, 1255, 1112.

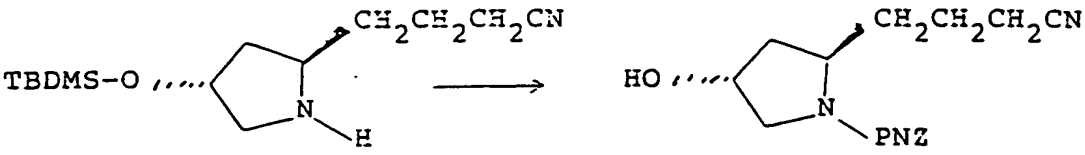
Reference Example 45



(2R,4R)-1-Benzyloxycarbonyl-2-(3-cyanopropyl)-4-t-butyldimethylsilyloxypyrrolidine (1.69 g) was dissolved in 34 ml of ethanol, and 338 mg of 5 % palladium-carbon was added thereto, followed by hydrogenation at room temparature under 1 atm. for 2 hours. The catalyst was removed by filtration, and the filtrate was distilled to obtain (2R,4R)-2-(3-cyanopropyl)-4-t-butyldimethylsilyloxypyrrolidine.

IR $\overset{neat}{max}$ cm^{-1}: 2245, 1460, 1250, 1080

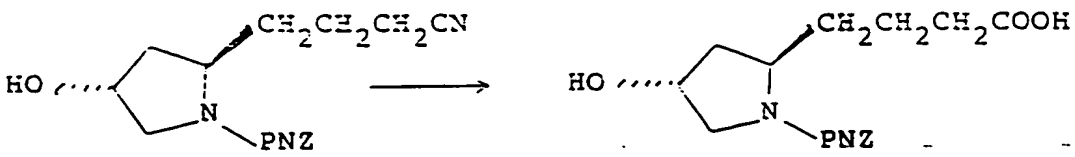
Reference Example 46



(2R,4R)-2-(3-Cyanopropyl)-4-t-butyldimethylsilyloxypyrrolidine (1.02 g) was dissolved in 22 ml of dioxane and 15.5 ml of water, and 7 ml of 4N sodium hydroxide solution was added thereto, followed by refluxing for 2 hours. The reaction mixture was neutralized with 6N hydrochloric acid and distilled to remove the solvent. The residue was dissolved in 10 ml of water, and 0.98 ml of triethylamine and a solution of 1.67 g of 2-(p-nitrobenzyloxycarbonyl)thio-4,6-dimethylpyrimidine in 20 ml of dimethylformamide were added thereto, followed by stirring at room temparature for 5 hours. The reaction mixture was diluted with ethyl acetate, washed successively with brine, dilute hydrochloric acid and brine, dried over anhydrous sodium sulfate and distilled to remove the solvent. The rsidue was purified by silica gel column chromatography to obtain (2R,4R)-1-(p-nitrobenzyloxy)carbonyl-2-(3-cyanopropyl)-4-hydroxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 2250, 1700, 1520, 1402, 1345.

Reference Example 47

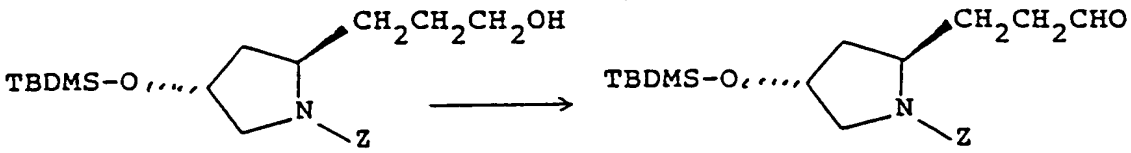


Following the procedure as in Reference Example 9 but using (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(3-cyano-

propyl)-4-hydroxypyrrolidine as the starting material, (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(3-carboxypropyl)-4-hydroxypyrrolidine was obtained.

IR ν_{max}^{neat} cm^{-1}: 1700, 1618 (sh), 1518, 1402, 1343.

Reference Example 48

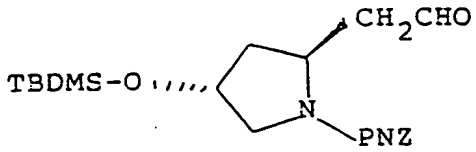


Oxalyl chloride (0.32 ml) was dissolved in 7.9 ml of dry dichloromethane, and 0.56 ml of dry dimethylsulfoxide was added thereto at -45 to -56°C in a nitrogen stream, followed by stirring at the same temperature for 20 minutes. To the reaction mixture was added a solution of 1.30 g of (2R,4R)-1-benzyloxycarbonyl-2-(3-hydroxypropyl)-4-t-butyldimethylsilyloxypyrrolidine in 6.2 ml of dry dichloromethane at -50 to -60°C, followed by stirring at the same temparature for 15 minutes. Then, 2.2 ml of triethylamine was added thereto at -50 to -60°C. The temparature was elevated to room temperature, and the reaction mixture was washed successively with brine, dilute hydrochloric acid and brine, dried over anhydrous sodium sulfate and distilled to obtain (2R,4R)-1-benzyloxycarbonyl-2-(2-formylethyl)-4-t-butyldimethylsilyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1703, 1413, 1359, 1255, 1110.

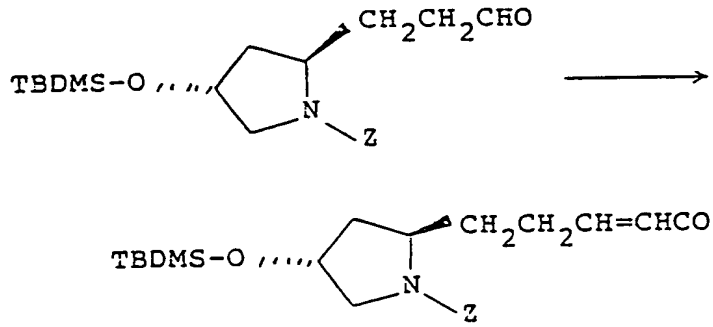
In the same procedure as above, (2S,4R)-1-p-nitrobenzyloxycarbonyl-2-formylmethyl-4-t-butyldimethylsilyloxypyrrolidine was obtained from (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(2-hydroxyethyl)-4-t-butyldimethylsilyloxy-

pyrrolidine.



IR ν_{max}^{neat} cm^{-1}: 1723 (sh), 1703, 1520, 1400, 1342.

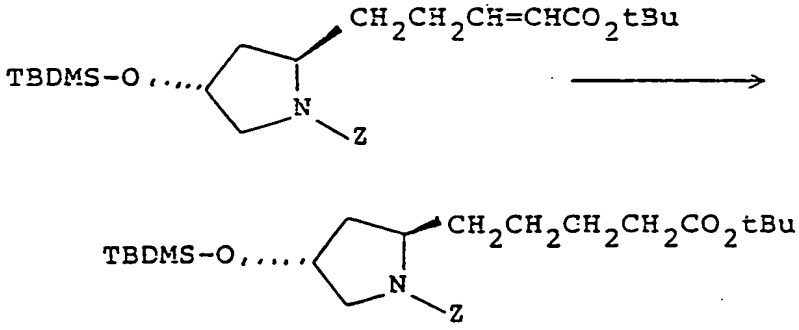
Reference Example 49



t-Butyloxycarbonylmethyltriphenylphosphonium bromide (2.15 g) was dissolved in 40 ml of dichloromethane, and 30 ml of a saturated sodium bicarbonate solution was added thereto, followed by stirring at room temperature for 5 minutes. The dichloromethane layer was separated and dried over anhydrous sodium sulfate. After filtration, a solution of 1.29 g of (2R,4R)-1-benzyloxycarbonyl-2-(2-formylethyl)-4-t-butyldimethylsilyloxypyrrolidine in 30 ml of dichloromethane was added to the filtrate, followed by refluxing for 30 minutes. After removal of the solvent, the residue was purified by silica gel column chromatography to obtain (2R,4R)-1-benzyloxycarbonyl-2-(3-t-butoxycarbonyl-methylidenepropyl)-4-t-butyldimethylsilyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1702, 1649, 1408, 1363, 1148.

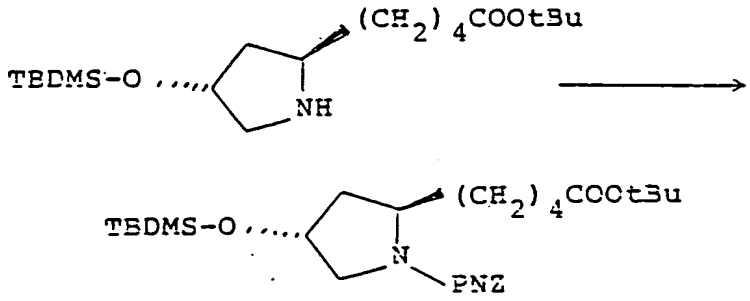
Reference Example 50



(2R,4R)-1-Benzyloxycarbonyl-2-(3-t-butoxycarbonyl-methylidenepropyl)-4-t-butyldimethylsilyloxypyrrolidine (1.17 g) was dissolved in 24 ml of ethanol, and 350 mg of 5 % palladium carbon was added thereto, followed by hydrogenation at room temperature under 1 atm for 3 hours. The catalyst was removed by filtration, and the filtrate was distilled to obtain (2R,4R)-2-(4-t-butoxycarbonylbutyl)-4-t-butyldimethylsilyloxypyrrolidine.

IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1730, 1460, 1365, 1250, 1147.

Reference Example 51

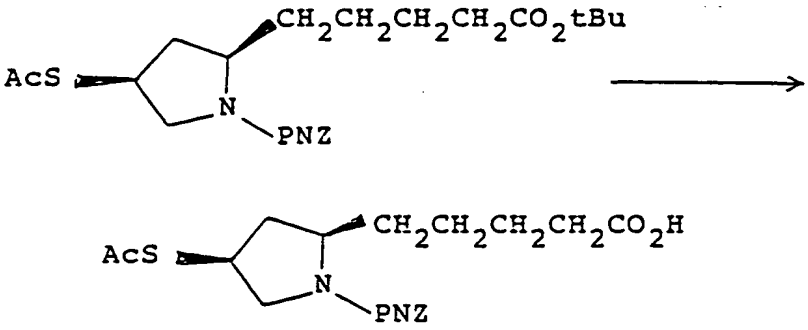


S-p-Nitrobenzyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine (719 mg) was added to 770 mg of (2R,4R)-2-(4-t-butoxycarbonylbutyl)-4-t-butyldimethylsilyloxypyrrolidine in 7 ml of tetrahydrofuran and stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl

acetate, washed successively with brine, dilute hydrochloric acid and brine, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel chromatography to obtain (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(4-t-butoxycarbonylbutyl)-4-t-butyldimethylsilyloxypyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1730 (sh), 1712, 1528, 1402, 1350.

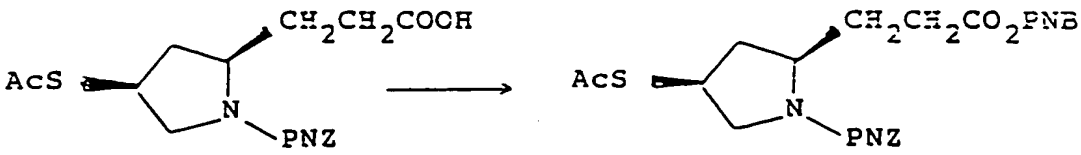
Reference Example 52



(2R,4S)-1-p-Nitrobenzyloxycarbonyl-2-(4-t-butyloxycarbonylbutyl)-4-acetylthiopyrrolidine (493 mg) was dissolved in 2.5 ml of trifluoroacetic acid, followed by stirring at room temperature for 15 minutes. The reaction mixture was distilled off to obtain (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-(4-carboxybutyl)-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1702, 1520, 1402, 1343.

Reference Example 53

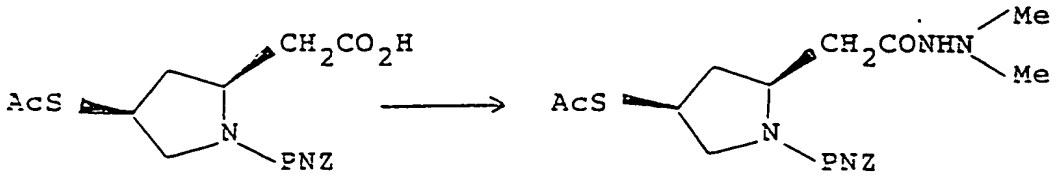


(2R,4S)-1-p-Nitrobenzyloxycarbonyl-2-(2-carboxyethyl)-4-acetylthiopyrrolidine (323 mg) was dissolved in 3.3

ml of dry dimethylformamide, and 150 mg of triethylamine and 324 mg of p-nitrobenzyl bromide were added thereto, followed by stirring at room temperature for 3.5 hours. To the reaction mixture was added water, and the resulting mixture was extracted with ethyl acetate, washed successively with a saturated sodium bicarbonate solution, water, dilute hydrochloric acid and water, dried over anhydrous sodium sulfate and distilled off to remove the solvent. The residue was purified by silica gel column chromatography to obtain (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-(2-p-nitrobenzyloxycarbonylethyl)-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1732, 1697, 1515, 1393, 1342.

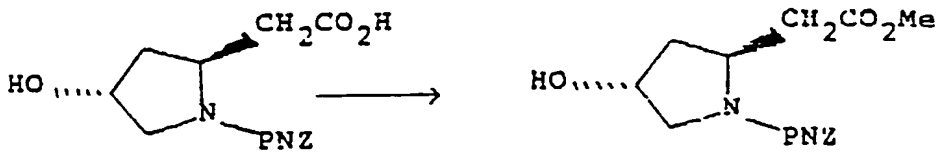
Reference Example 54



(2R,4S)-1-p-Nitrobenzyloxycarbonyl-2-carboxymethyl-4-acetylthiopyrrolidine (218 mg) was dissolved in 2.2 ml of dry tetrahydrofuran, and 63 mg of N,N-dimethylhydrazine and 159 mg of N,N-dicyclohexylcarbodiimide were added thereto, followed by stirring at room temperature for 3 hours. After any insoluble material was removed by filtration, the filtrate was distilled to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-[(N,N-dimethylhydrazinocarbonyl)methyl]-4-acetylthiopyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1700, 1660, 1515, 1418, 1340.

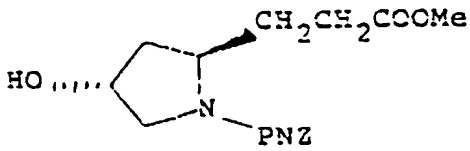
Reference Example 55



(2R,4R)-1-p-Nitrobenzyloxycarbonyl-2-carboxymethyl-4-hydroxypyrrolidine (5.39 g) was dissolved in 54 ml of dry methanol, and 0.9 ml of conc. sulfuric acid was added thereto, followed by refluxing for 4 hours. The reaction mixture was neutralized with 1N sodium hydroxide solution and distilled to remove the solvent. To the residue was added ethyl acetate, and the mixture was washed with water, dried over anhydrous sodium sulfate and distilled to obtain (2S,4R)-1-p-nitrobenzyloxycarbonyl-2-methoxycarbonylmethyl-4-hydroxypyrrolidine.

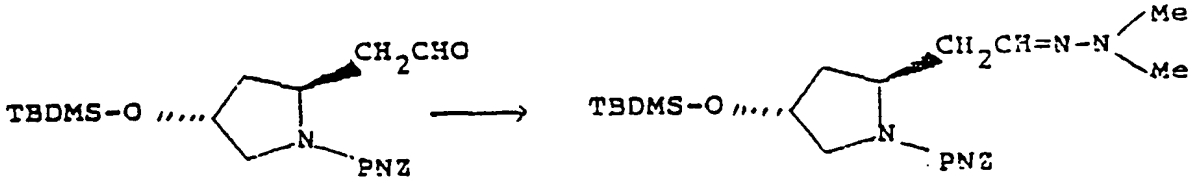
IR ν_{max}^{neat} cm^{-1}: 1740, 1708, 1525, 1440, 1348.

In the same procedure as above, (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(2-methoxycarbonylethyl)-4-hydroxypyrrolidine was obtained from (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(2-carboxyethyl)-4-hydroxypyrrolidine.



IR ν_{max}^{neat} cm^{-1}: 1730, 1688, 1523, 1352.

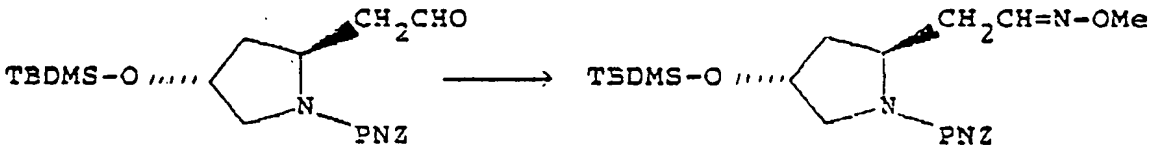
Reference Example 56



(2S,4R)-1-p-Nitrobenzyloxycarbonyl-2-formylmethyl-4-t-butyldimethylsilyloxypyrrolidine (423 mg) was dissolved in 2 ml of ethanol, and 65 mg of N,N-dimethylhydrazine was added thereto, followed by stirring at room temperature for 15 minutes. To the reaction mixture was added ethyl acetate, and the mixture was washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(2-dimethylhydrazinoethyl)-4-t-butyldimethylsilyloxy-pyrrolidine.

IR ν_{max}^{neat} cm^{-1}: 1713, 1528, 1405, 1348.

Reference Example 57

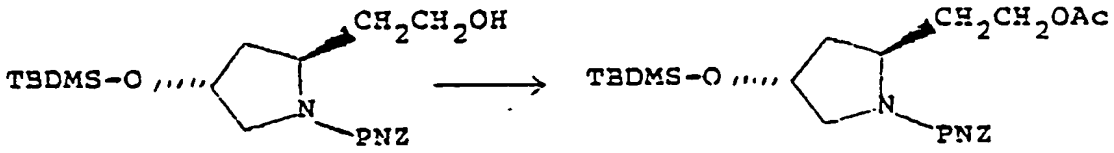


Methoxyamine hydrochloride (124 mg) was dissolved in 4 ml of water, and sodium acetate (244 mg) and a solution of 418 mg of (2S,4R)-1-p-nitrobenzyloxycarbonyl-2-formyl-methyl-4-t-butyldimethylsilyloxypyrrolidine in 5 ml of ethanol were added thereto at room temperature, followed by stirring at the same temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed successively with water and a saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2R,4R)-1-p-nitro-benzyloxy-2-(2-methoxyimino)ethyl-4-t-butyldimethylsilyoxy-

pyrrolidine.

IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1705, 1523, 1400, 1343.

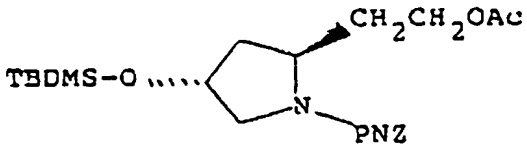
Reference Example 58



(2R,4R)-1-p-Nitrobenzyloxycarbonyl-2-(2-hydroxyethyl)-4-t-butyldimethylsilyloxypyrrolidine (900 mg) was dissolved in 2.25 ml of dry pyridine, and 2.25 ml of acetic anhydride was added to the solution at room temperature, followed by stirring for 1 hour. The reaction mixture was diluted with diethyl ether, washed successively with brine, a diluted aqueous hydrochloric acid, brine, a diluted aqueous sodium hydroxide solution and brine, dired over anhydrous sodium sulfate to give (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(2-acetoxyethyl)-4-t-butyldimethylsilyloxypyrrolidine.

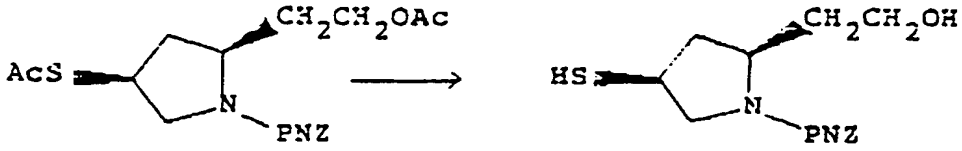
IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1730, 1705, 1522, 1408, 1350.

In the same procedure as above, (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(3-acetoxypropyl)-4-t-butyldimethylsilyloxypyrrolidine was obtained from (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-(3-hydroxypropyl)-4-t-butyldimethylsilyloxypyrrolidine.



IR $\overset{\text{neat}}{\underset{\text{max}}{}}$ cm^{-1}: 1739, 1712, 1522, 1401, 1345.

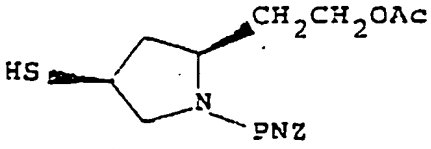
Reference Example 59



(2R,4S)-1-p-Nitrobenzyloxycarbonyl-2-(2-acetoxyethyl)-4-acetylthiopyrrolidine (204 mg) was dissolved in 5 ml of methanol and 1 ml of 1N sodium hydroxide solution was added thereto at room temperature under nitrogen stream, followed by stirring for 30 minutes. 1H Hydrochloric acid (1.2 ml) was added to the reaction mixture. The resulting mixture was diluted with ethyl acetate, washed with brine five times, dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by silica gel thin layer chromatogaraphy to give (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-(2-hydroxyethyl)-4-mercaptopyrrolidine.

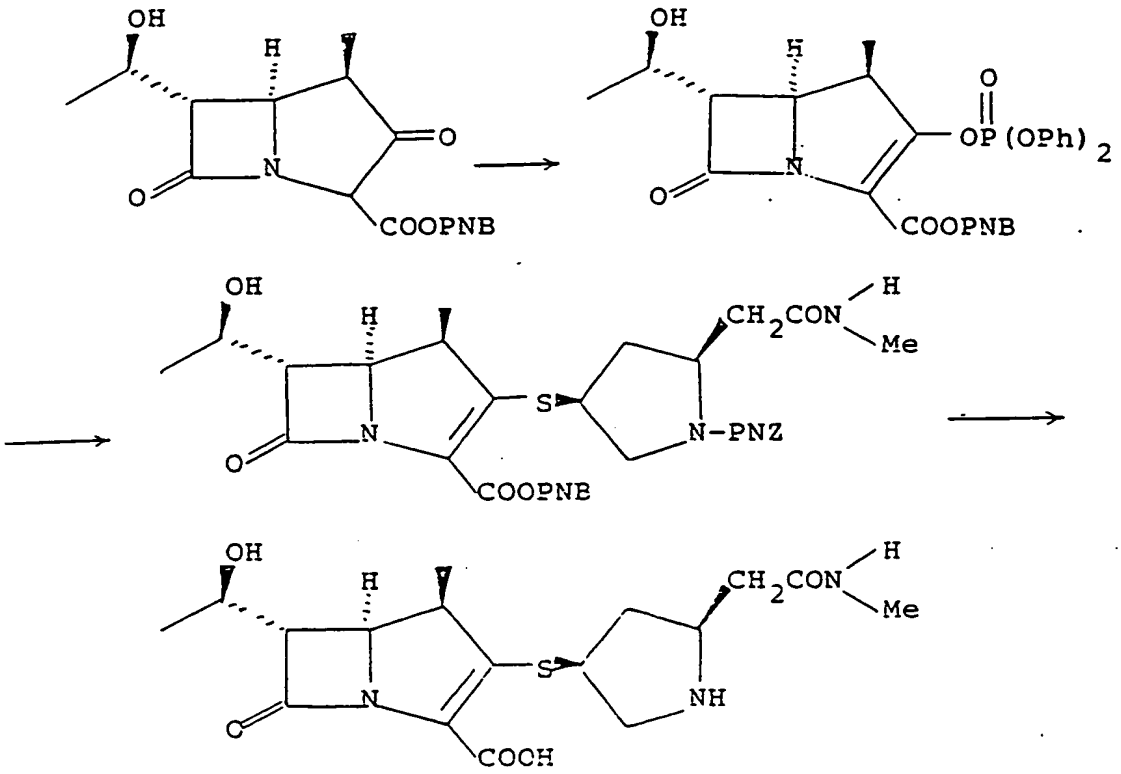
IR ν_{max}^{neat} cm^{-1}: 1690, 1522, 1432, 1408, 1348.

In the same procedure as above, (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-(3-hydroxypropyl)-4-mercaptopyrrolidine was obtained from (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-(3-acetoxypropyl)-4-mercaptopyrrolidine.



IR ν_{max}^{neat} cm^{-1}: 1695, 1522, 1433, 1410, 1350.

Example 1



a) (4R,5R,6S,8R)-p-Nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-3,7-dione-2-carboxylate (511 mg) was dissolved in 3.1 ml of dry acetonitrile and 154 mg of diisopropylethylamine. A solution of 317 mg of diphenyl chlorophosphate in 1 ml of dry acetonitrile was added thereto in a nitrogen stream under ice-cooling, followed by stirring for 1 hour. The mixture was cooled at -35°C, and 154 mg of diisopropylethylamine and 420 mg of (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-methylaminocarbonylmethyl-4-mercaptopyrrolidine were added thereto, followed by stirring at -20 to -30°C for 1 hour. The reaction mixture was diluted with ether-dichloromethane (4:1), washed successively with water, an aqueous potassium dihydrogen phosphate solution and water, dried over an-

hydrous magnesium sulfate and concentrated. The residue was purified by silica gel thin layer chromatography to obtain 453 mg of (4R,5S,6S,8R,2'R,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-methylaminocarbonylmethylpyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate.

IR ν_{max}^{neat} cm^{-1}: 1762, 1700, 1655, 1520, 1403, 1343, 1212.

NMR δ ($CDCl_3$): 1.27 (3H, d, J = 7Hz), 1.34 (3H, d, J = 6.2Hz), 2.76 (3H, d, J = 4.6Hz), 5.21 (2H,s), 5.47 (1H, d, J = 13.6Hz), 6.94 (1H, bs), 8.18 (4H, d, J = 8.8Hz).

b) (4R,5S,6S,8R,2'R,4'S)-p-Nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-methylaminocarbonylmethyl-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (453 mg) was dissolved in 21 ml of tetrahydrofuran. A morpholinopropanesulfonic acid buffer solution (pH 7.0) (14 ml) and 10 % palladium-carbon (obtained by hydrogenation in water under atmospheric pressure of hydrogen at room temperature for 1 hour, filtration and washing with water) (549 mg) were added thereto. The resultant mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 3 hours. The catalyst was removed by filtration, and the filtrate was distilled under reduced pressure to remove tetrahydrofuran. The residual solution was washed with dichloromethane, and the aqueous layer was again distilled

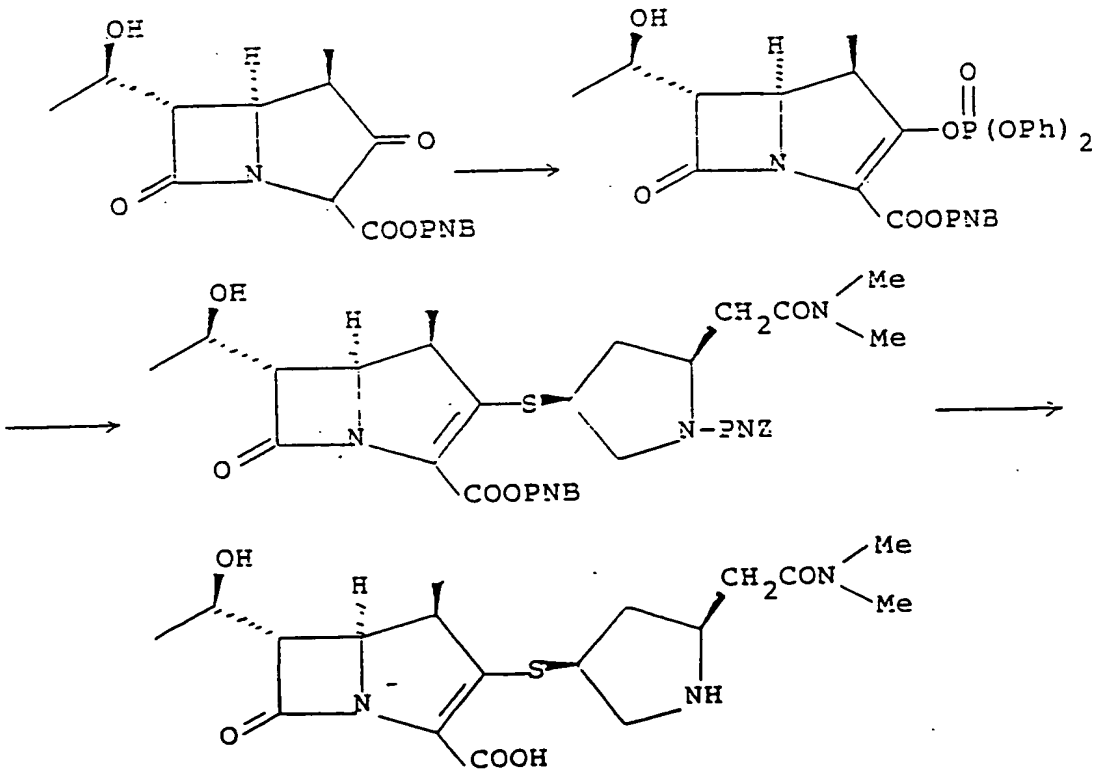
under reduced pressure to remove the organic solvent. The residual solution was subjected to polymer chromatography (CHP-20P) to obtain (4R,5S,6S,8R,2'R,4'S)-3-[(2-methyl-aminocarbonylmethylpyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with 1 % tetra-hydrofuran-water.

UV $\lambda_{max}^{H_2O}$ nm: 298.

IR ν_{max}^{KBr} cm^{-1}: 1748, 1650, 1585, 1380, 1250.

NMR δ (D_2O): 1.19 (3H, d, J = 7Hz), 1.27 (3H, d, J = 6Hz), 2.72 (3H, s), 2.79 (2H, d, J = 7Hz), 3.44 (1H, dd, J = 2.6Hz and 6Hz), 4.19 (1H, d, J = 2.6Hz).

Example 2



a) (4R,5R,6S,8R)-p-Nitrobenzyl-4-methyl-6-(1-

hydroxyethyl)-1-azabicyclo[3.2.0]-hept-3,7-dione-2-carboxylate (98 mg) was dissolved in 1 ml of dry acetonitrile and diisopropylethylamine (39 mg). A solution of 81 mg of diphenyl chlorophosphate in 0.5 ml of dry acetonitrile was added thereto in a nitrogen stream under ice-cooling, followed by stirring for 1 hour. The mixture was cooled at -35°C, and 35 mg of diisopropylethylamine and a solution of 99 mg of [2R,4S]-1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonylmethyl-4-mercaptopyrrolidine in 1 ml of dry acetonitrile were added thereto, followed by stirring at -20 to -30°C for 1 hour. The mixture was diluted with ether-dichloromethane (4:1), washed successively with water, an aqueous potassium dihydrogen phosphate solution and water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel thin layer chromatography to obtain 88 mg of (4R,5S,6S,8R,2'R,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonylmethylpyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate.

IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1690, 1520, 1400, 1345, 1105.

NMR δ ($CDCl_3$): 1.28 (3H, d, J = 6.8Hz), 1.36 (3H, d, J = 7Hz), 5.22 (2H, s), 5.49 (1H, d, J = 13.9Hz), 8.21 (4H, d, J = 8.8Hz).

b) (4R,5S,6S,8R,2'R,4'S)-p-Nitrobenzyl-3-[(1-p-nitrobenzyloxycarbony-2-dimethylaminocarbonylmethyl-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabi-

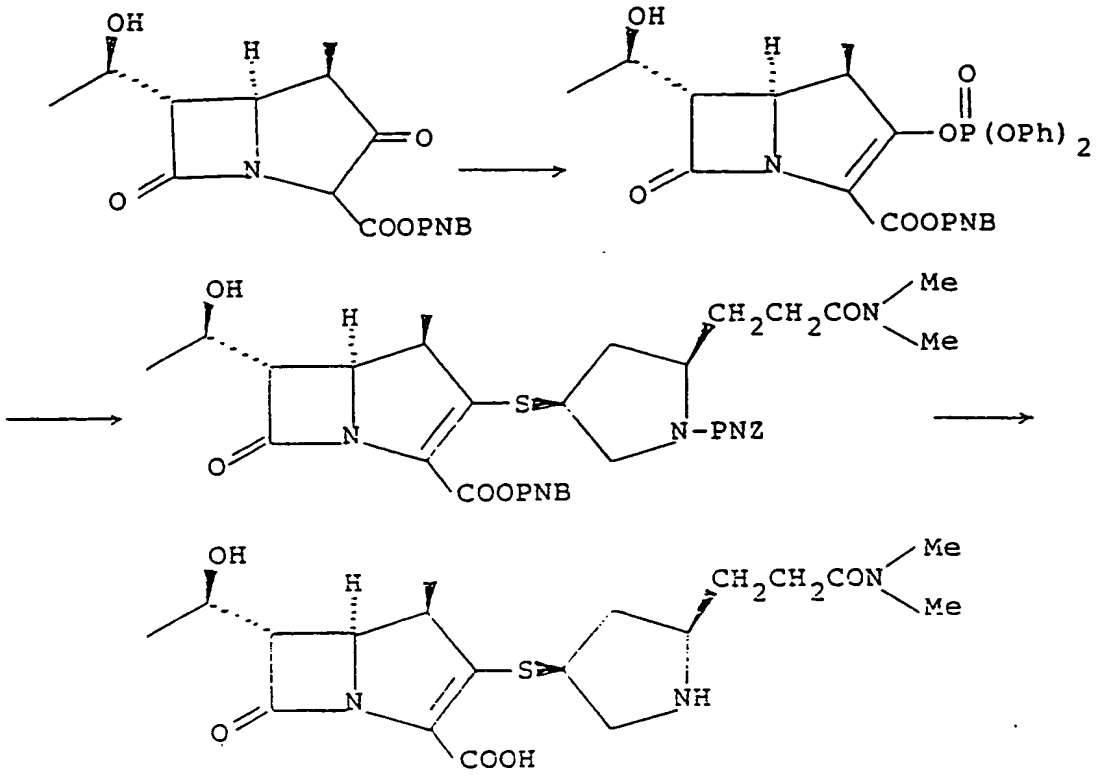
cyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (83 mg) was dissolved in 3.7 ml of tetrahydrofuran, and a morpholino-propanesulfonic acid buffer solution (pH 7.0) (2.4 ml) and 10 % palladium-carbon as prepared in Example 1 b) (101 mg) were added thereto. The resulting mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 3 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residual solution was washed with dichloromethane, and the aqueous layer was again distilled under reduced pressure to remove the organic solvent. The residual solution was subjected to polymer chromatography (CHP-20P) to obtain (4R,5S,6S,8R,2'R,4'S)-3-[(2-dimethylaminocarbonylmethyl-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-aza-bicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with 1 % tetrahydrofuran-water.

UV $\lambda_{max}^{H_2O}$ nm: 296.

IR ν_{max}^{KBr} cm^{-1}: 1752, 1630, 1390, 1260, 1148.

NMR δ (D_2O): 1.20 (3H, d, J = 6.9 Hz), 1.27 (3H, d, J = 6.3 Hz), 2.91 (3H, s), 3.02 (3H, s).

Example 3



a) (4R,5R,6S,8R)-p-Nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-3,7-dione-2-carboxylate (101 mg) was dissolved in 1.5 ml of dry acetonitrile and 37 mg of diisopropylethylamine. A solution of 77 mg of diphenyl chlorophosphate in 0.8 ml of dry acetonitrile was added thereto in a nitrogen stream under ice-cooling, followed by stirring for 1 hour. The mixture was cooled at -35°C, and 40 mg of diisopropylethylamine and a solution of 117 mg of (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-(2-dimethylaminocarbonylethyl)-4-mercaptopyrrolidine in 1 ml of dry acetonitrile were added thereto, followed by stirring for 1 hour at -20 to -30°C. The reaction mixture was diluted with ether-dichloromethane (4:1), washed successively with water, an aqueous potassium dihydrogen

phosphate solution and water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel thin layer chromatography to obtain 90 mg of (4R,5S,6S,8R,2'R,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-(2-dimethylaminocarbonylethyl)-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate.

IR ν_{max}^{neat} cm^{-1}: 1763, 1700, 1625, 1518, 1400, 1343.

NMR δ ($CDCl_3$): 1.26 (3H, d, J = 7.9Hz), 1.35 (3H, d , J = 6.4Hz), 2.91 (3H, s), 2.95 (3H, s), 5.21 (2H, s), 5.48 (1H, d, J = 13.6Hz), 8.20 (4H, d, J = 8.8Hz).

b) (4R,5S,6S,8R,2'R,4'S)-p-Nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(2-dimethylaminocarbonylethyl)-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (90 mg) was dissolved in 4 ml of tetrahydrofuran. A morpholinopropanesulfonic acid buffer solution (pH 7.0) (2.7 ml) and 10 % palladium-carbon as prepared in Example 1 b) (109 mg) were added thereto. The resulting mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 3 hours. The catalyst was removed by filtration, and the filtrate was distilled under reduced pressure to remove tetrahydrofuran. The residual solution was washed with dichloromethane, and the aqueous layer was again distilled under redued pressure to remove the organic solvent. The residual solution was subjected to polymer chromatography

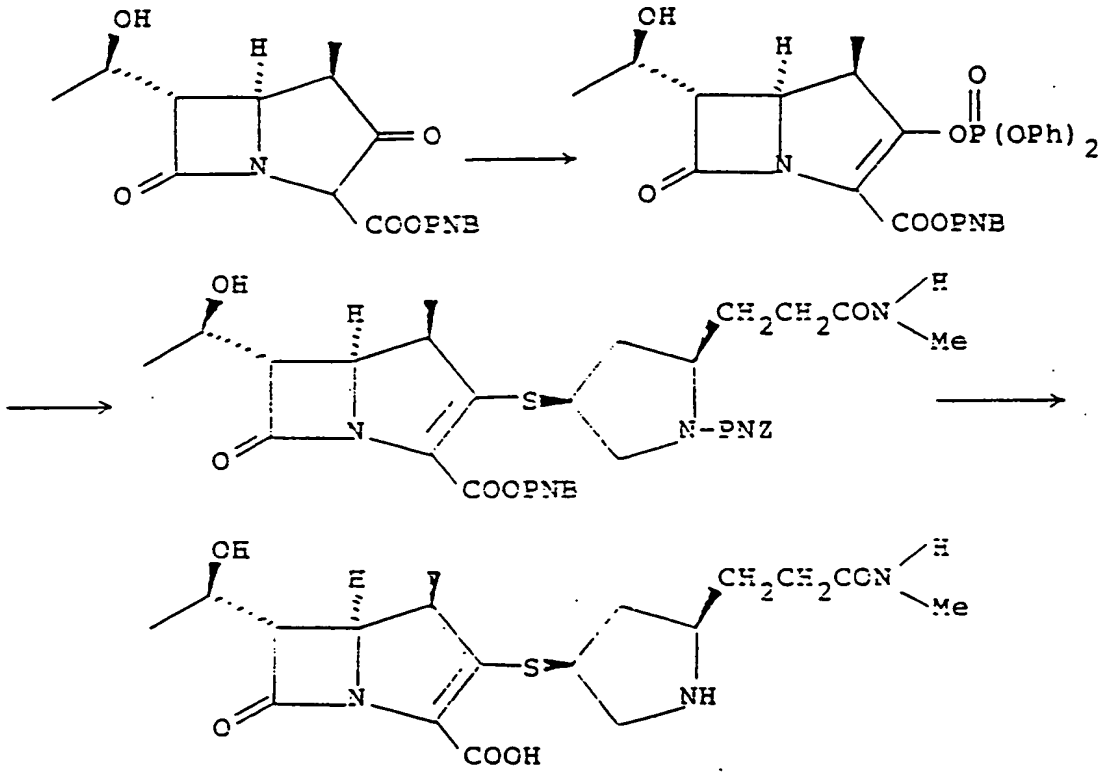
(CHP-20P) to obtain (4R,5S,6S,8R,2'R,4'S)-3-[[2-(2-dimethylaminocarbonylethyl)pyrrolidin]-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with 1 % tetrahydrofuran-water.

UV $\lambda_{max}^{H_2O}$ nm: 298.

IR ν_{max}^{KBr} cm^{-1}: 1757, 1620, 1385, 1260, 1145.

NMR δ (D_2O): 1.18 (3H, d, J = 7.3Hz), 1.26 (3H, d, J = 6.3Hz), 2.90 (3H, s), 3.03 (3H, s).

Example 4



a) (4R,5R,6S,8R)-p-Nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-3,7-dione-2-carboxylate (78 mg) was dissolved in 1 ml of dry acetonitrile and 29 mg of diisopropylethylamine. A solution of 59 mg of diphenyl chlorophosphate in 0.6 ml of dry aceto-

nitrile was added thereto in a nitrogen stream under ice-cooling, followed by stirring for 1 hour. The mixture was cooled at -35°C, and 26 mg of diisopropylethylamine and a solution of 72 mg of (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-(2-methylaminocarbonylethyl)-4-mercaptopyrrolidine in 1 ml of dry acetonitrile were added thereto, followed by stirring at -20 to -30°C for 1 hour. The reaction mixture was diluted with ether-dichloromethane (4:1), washed successively with water, an aqueous potassium dihydrogen phosphate solution and water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel thin layer chromatography to obtain 68 mg of (4R,5S,6S,8R,2'R,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-(2-methylaminocarbonylethyl)pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate.

IR $\overset{CHCl_3}{max}$ cm^{-1}: 1767, 1695, 1518, 1400, 1341.

NMR δ (acetone-d_6): 1.27 (3H, d, J = 5.9Hz), 1.28 (3H, d, J = 7Hz), 2.68 (3H, d, J = 4.6Hz), 5.26 (2H, s).

b) (4R,5S,6S,8R,2'R,4'S)-p-Nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-(2-methylaminocarbonylethyl)-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylte (68 mg) was dissolved in 2.8 ml of 25 % dimethylformamide-tetrahydrofuran. A morpholinopropanesulfonic acid buffer solution (pH 7.0) (1.4 ml) and 10 % palladium-carbon as prepared in Example 1 b) (83 mg) were added thereto. The resulting

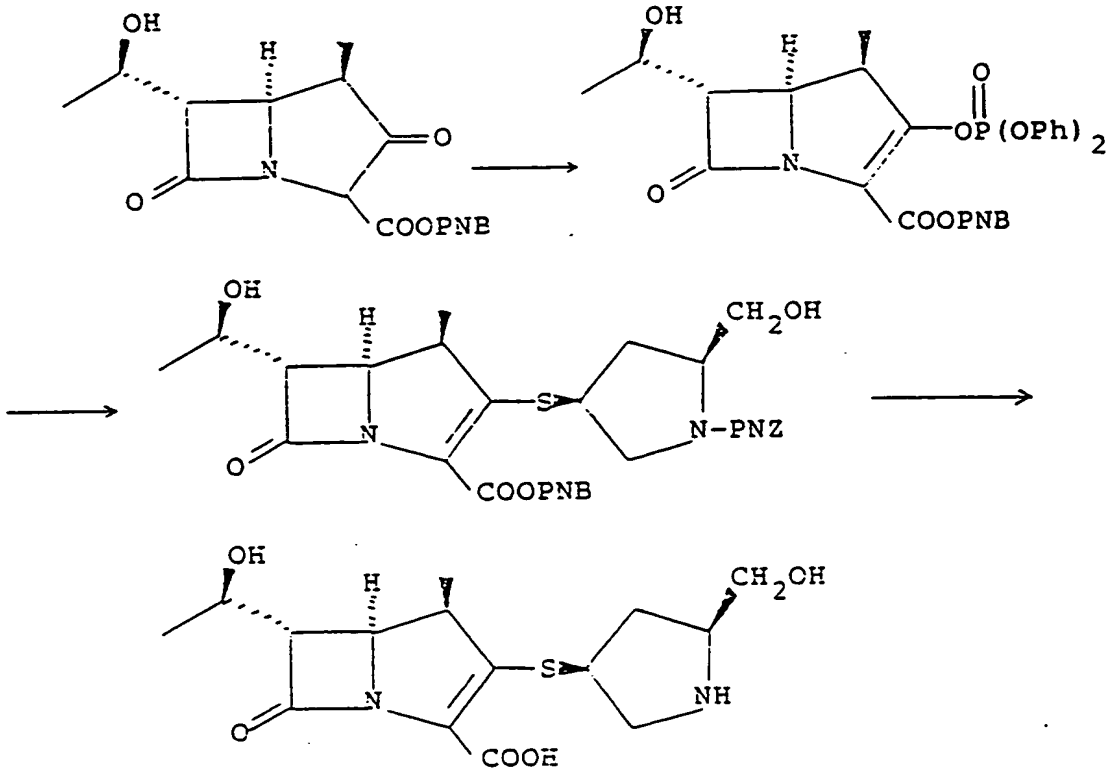
mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 3 hours. The catalyst was removed by filtration, and the filtrate was distilled under reduced pressure to remove tetrahydrofuran. The residual solution was washed with dichloromethane, and the aqueous layer was again distilled under reduced pressure to remove the organic solvent. The residual solution was subjected to polymer chromatography (CHP-20P) to obtain (4R,5S,6S,8R,2'R,4'S)-3-[(2-(2-methylaminocarbonylethyl)-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with 1 % tetrahydrofuran-water.

UV $\overset{H_2O}{max}$ nm: 299.

IR $\overset{KBr}{max}$ cm^{-1}: 1751, 1640, 1592, 1382, 1253.

NMR δ (D_2O): 1.19 (3H, d, J = 7.3 Hz), 1.27 (3H, d, J = 6.3Hz), 2.71 (3H, s), 3.44 (1H, dd, J = 1.7Hz and 5.9Hz).

Example 5



a) (4R,5R,6S,8R)-p-Nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-3,7-dione-2-carboxylate (123 mg) was dissolved in 2 ml of dry acetonitrile and 45 mg of diisopropylethylamine. A solution of 93 mg of diphenyl chlorophosphate in 1 ml of dry acetonitrile was added thereto in a nitrogen stream under ice-cooling, followed by stirring for 1 hour. The mixture was cooled at -35°C, and 49 mg of diisopropylethylamine and a solution of 117 mg of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-hydroxymethyl-4-mercaptopyrrolidine in 1 ml of dry acetonitrile were added thereto, followed by stirring at -20 to -30°C for 1 hour. The reaction mixture was diluted with ether-dichloromethane (4:1), washed successively with water, an aqueous potassium dihydrogen phosphate solution and water, dried over anhydrous magnesium sulfate and concen-

trated. The residue was purified by silica gel thin layer chromatography to obtain 136 mg of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-hydroxymethyl-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabi-cyclo[3.2.0]-hept-2-en-7-one-2-carboxylate.

IR ν_{max}^{neat} cm^{-1}: 1762, 1695, 1518, 1340, 1210.

NMR δ ($CDCl_3$): 1.27 (3H, d, J = 6.4Hz), 1.33 (3H, d, J = 5.7Hz), 5.22 (2H, s), 5.46 (1H, d, J = 13.9Hz), 8.18 (4H, d, J = 8.6Hz).

b) (4R,5S,6S,8R,2'S,4'S)-p-Nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-hydroxymethylpyrrolidin)-4-yl-thio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (136 mg) was dissolved in 6 ml of tetrahydrofuran. A morpholinopropanesulfonic acid buffer solution (pH 7.0) (4 ml) and 10 % palladium-carbon as prepared in Example 1 b) (165 mg) were added thereto. The resultant mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 3 hours. The catalyst was removed by filtration, and the filtrate was distilled under reduced pressure to remove tetrahydrofuran. The residual solution was washed with dichloromethane, and the aqueous layer was again distilled under reduced pressure to remove the organic solvent. The residual solution was subjected to polymer chromatography (CHP-20P) to obtain (4R,5S,6S,8R,2'S,4'S)-3-(2-hydroxymethylpyrrolidin)-4-yl-thio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted

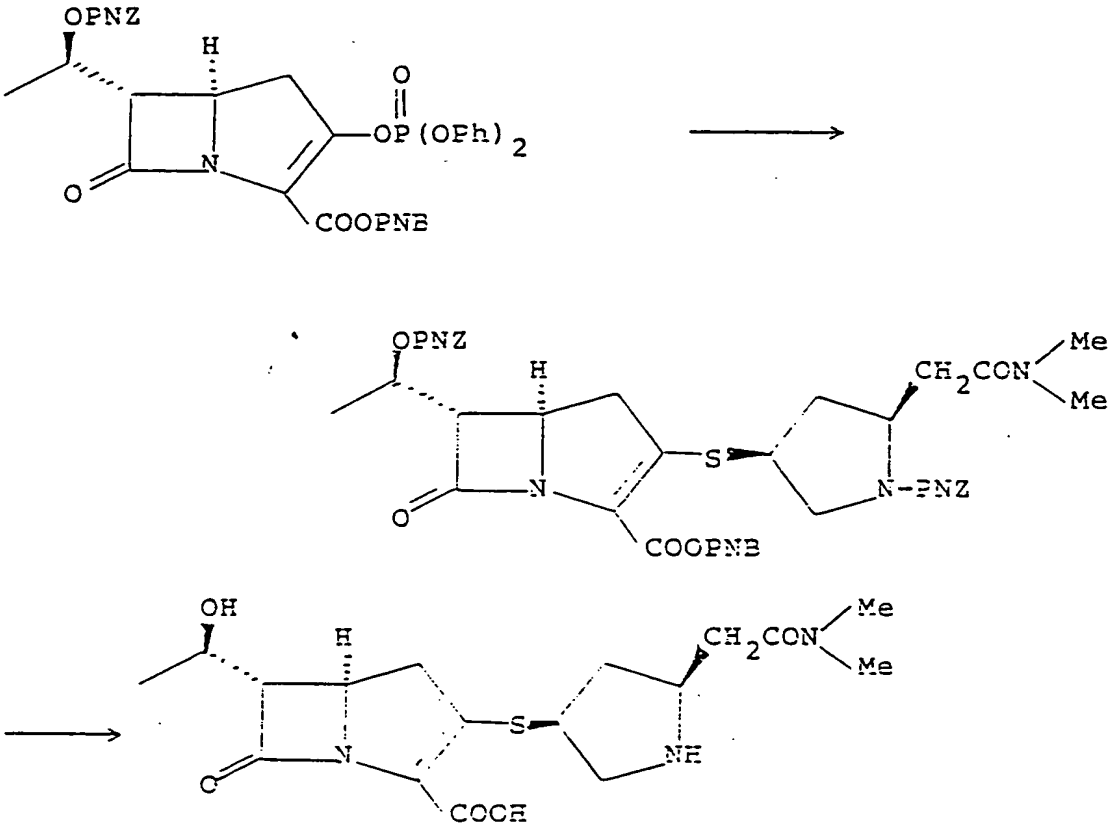
with 1 % tetrahydrofuran-water.

UV $\lambda_{max}^{H_2O}$ nm: 298.

IR ν_{max}^{KBr} cm^{-1}: 1748, 1585, 1386, 1252.

NMR δ (D_2O): 1.20 (3H, d, J=7.3 Hz), 1.27 (3H, d, J=6.3 Hz).

Example 6



a) (5R,6S,8R)-p-Nitrobenzyl-3-(diphenylphosphoryloxy)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (182 mg) was dissolved in 2 ml of dry acetonitrile, and 34 mg of diisopropylethylamine and 88 mg of [2R,4S]-1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonylmethyl-4-mercaptopyrrolidine were added thereto in a nitrogen stream

under ice-cooling, followed by stirring for 15 minutes. The reaction mixture was diluted with ether-dichloromethane, washed successively with water, an aqueous potassium dihydrogen phosphate solution and water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel thin layer chromatography to obtain 135 mg of (5R,6S,8R,2'R,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonylmethylpyrrolidin)-4-ylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate.

IR $\overset{CHCl_3}{max}$ cm^{-1}: 1780, 1743, 1700, 1630, 1517, 1255.

NMR δ ($CDCl_3$): 1.49 (3H, d, J=6.4 Hz), 2.92 (6H, s), 5.22 (2H, s), 5.26 (2H, s), 5.46 (1H, d, J = 13.9Hz), 8.22 (6H, d, J = 8.1Hz).

b) (5R,6S,8R,2'R,4'S)-p-Nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonylmethyl-pyrrolidin)-4-ylthio]-6-(1-p-nitrobenzyloxycarbonyloxy-ethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (135 mg) was dissolved in 5.1 ml of tetrahydrofuran, and a morpholinopropanesulfonic acid buffer solution (pH 7.0) (3.4 ml) and 10 % palladium-carbon as prepared in Example 1 b) (164 mg) were added thereto. The resultant mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 4 hours. The catalyst was removed by filtration, and the filtrate was distilled under reduced pressure to remove tetrahydrofuran. The residual solution

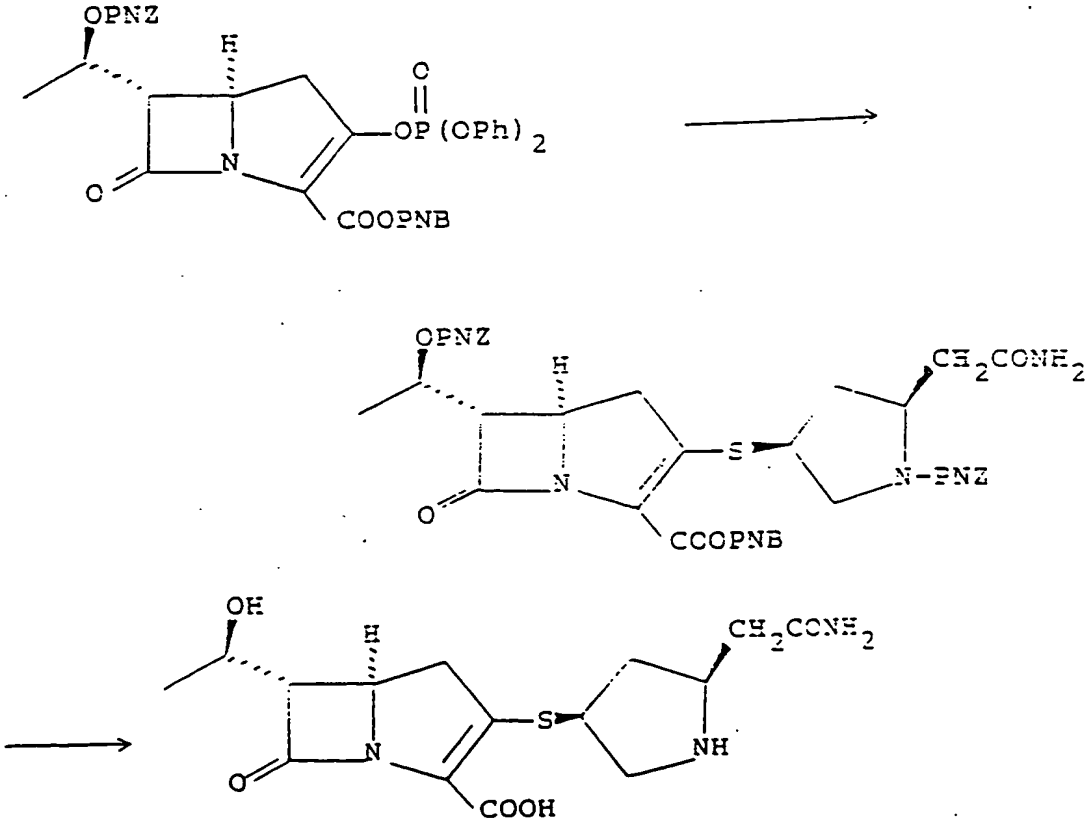
was washed with dichloromethane, and the aqueous layer was again distilled under reduced pressure to remove the organic solvent. The residual solution was subjected to polymer chromatography (CHP-20P) to obtain (5R,6S,8R,2'R,4'S)-3-[(2-dimethylaminocarbonylmethylpyrrolidin)-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with 1 % tetrahydrofuran-water.

UV $\overset{H_2O}{max}$ nm: 298.

IR $\overset{KBr}{max}$ cm^{-1}: 1752, 1620, 1580, 1380, 1240, 1140.

NMR δ (D_2O): 1.26 (3H, d, J = 6.3Hz), 2.91 (3H, s), 3.02 (3H, s).

Example 7



a) (5R,6S,8R)-p-Nitrobenzyl-3-(diphenylphos-

phoryloxy)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (167 mg) was dissolved in 2.5 ml of dry acetonitrile, and 54 mg of diisopropylethylamine and 85 mg of (2R,4S)-1-p-nitrobenzyloxycarbonyl-2-aminocarbonylmethyl-4-mercaptopyrrolidine were added thereto in a nitrogen stream under ice-cooling, followed by stirring for 15 minutes. The reaction mixture was diluted with ether-dichloromethane (4:1), washed successively with water, an aqueous potassium dihydrogen phosphate solution and water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel thin layer chromatography to obtain 60 mg of (5R,6S,8R,2'R,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-aminocarbonylmethylpyrrolidin)-4-ylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo-[3.2.0]-hept-2-en-7-one-2-carboxylate.

IR ν_{max}^{Nujol} cm^{-1}: 1775, 1740, 1690, 1670 (sh), 1510, 1340.

NMR δ (DMSO-d_6): 1.34 (3H, d, J = 6.2 Hz), 5.23 (2H, s), 5.30 (2H, s), 6.82 (1H, bs), 8.21 (6H, d, J = 8.8Hz).

b) (5R,6S,8R,2'R,4'S)-p-Nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-aminocarbonylmethylpyrrolidin)-4-ylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (60 mg) was dissolved in 1.3 ml of tetrahydrofuran and 0.5 ml of dimethylformamide, and a morpholinopropanesulfonic acid buffer solution (pH 7.0) (1.2 ml) and 10 % palladium-carbon as

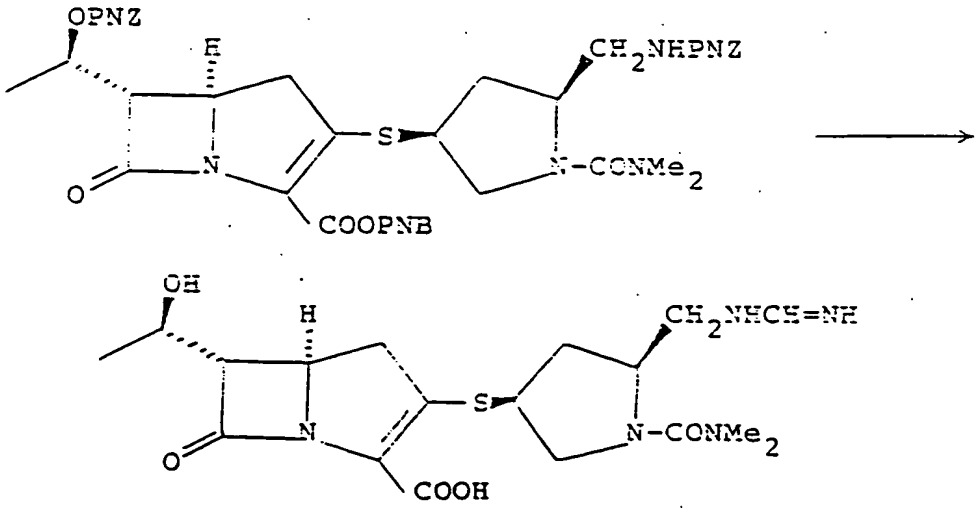
prepared in Example 1 b) (73 mg) were added thereto. The resultant mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 4 hours. The catalyst was removed by filtration, and the filtrate was distilled under reduced pressure to remove tetrahydrofuran. The residual solution was washed with dichloromethane, and the aqueous layer was again distilled under reduced pressure to remove the organic solvent. The residual solution was subjected to polymer chromatography (CHP-20P) to obtain (5R,6S,8R,2'R,4'S)-3-[(2-aminocarbonylmethylpyrrolidin)-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with 1 % tetrahydrofuran-water.

UV $\lambda_{max}^{H_2O}$ nm: 298.

IR ν_{max}^{KBr} cm^{-1}: 1743, 1670, 1590, 1400, 1260.

NMR δ (D_2O): 1.27 (3H, d, J = 6.3Hz).

Example 8



(5R,6S,8R,2'S,4'S)-p-Nitrobenzyl-3-[(1-demethyl-aminocarbonyl-2-p-nitrobenzyloxycarbonylaminomethyl-

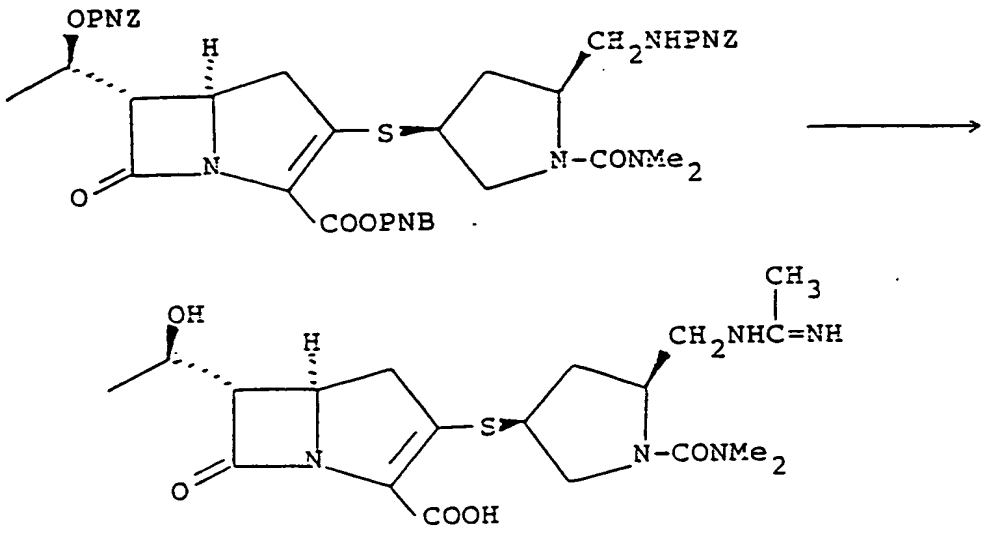
pyrrolidin)-4-ylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (100 mg) was dissolved in 10 ml of tetrahydrofuran, and 8.5 ml of a morpholinopropanesulfonic acid buffer solution (pH 7.0) and 10 % palladium-carbon as prepared in Example 1 b) (121 mg) were added thereto. The resultant mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 4 hours. The catalyst was removed by filtration, and the filtrate was cooled at 0°C and adjusted with 1N sodium hydroxide to pH 8.5, and then 200 mg of benzylform imidate hydrochloride was added thereto, followed by stirring for 10 minutes. Tetrahydrofuran in the reaction mixture was removed under reduced pressure. The residual solution was washed with dichloromethane, and the aqueous layer was again distilled under reduced pressure to remove the organic solvent. The residual solution was subjected to polymer chromatography (CHP-20P) to obtain (5R,6S,2'S,4'S)-3-[(1-methylpyrrolidin)-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with 1 % tetrahydrofuran-water.

UV $\lambda_{max}^{H_2O}$ nm: 298.

IR ν_{max}^{KBr} cm^{-1}: 1752, 1580, 1494, 1383, 1240.

NMR δ (D_2O): 1.25 (3H, d, J = 6.3Hz), 2.85 (6H, s), 7.78 (1H, s).

Example 9



(5R,6S,8R,2'S,4'S)-p-Nitrobenzyl-3-[(1-dimethylaminocarbonyl-2-p-nitrobenzyloxycarbonylaminomethylpyrrolidin)-4-ylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate (100 mg) was dissolved in 10 ml of tetrahydrofuran, and 8.5 ml of a morpholinopropanesulfonic acid buffer solution (pH 7.0) and 10 % palladium-carbon as prepared in Example 1 b) (121 mg) were added thereto, and the mixture was hydrogenated under atmospheric pressure of hydrogen at room temperature for 4 hours. The catalyst was removed by filtration, and the filtrate was cooled at 0°C and adjusted with 1N sodium hydroxide solution to pH 8.5. Ethylacetoimidate hydrochloride (250 mg) was added thereto, followed by stirring for 1 hour. Tetrahydrofuran in the reaction mixture was removed under reduced pressure. The residual solution was washed with dichloromethane, and the aqueous layer was again distilled under reduced pressure to remove the organic solvent. The residual solution was subjected to

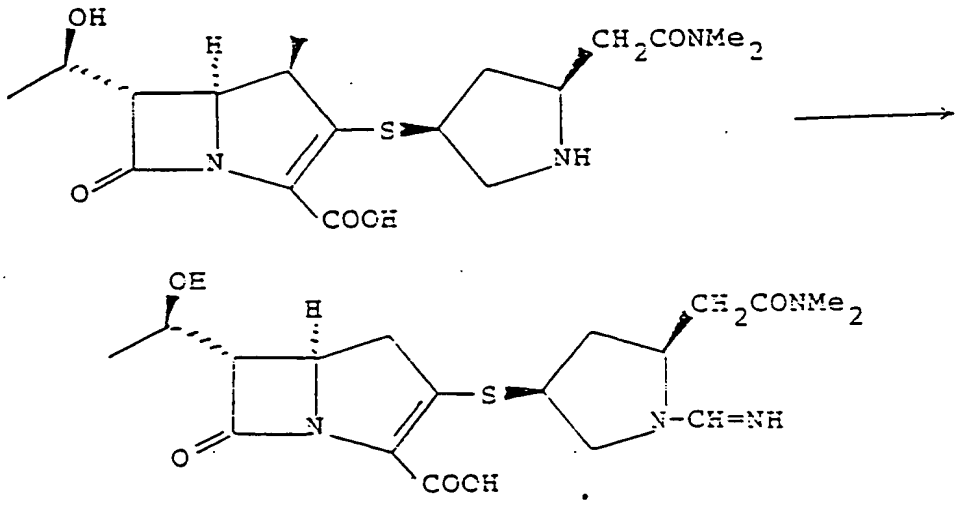
polymer chromatography (CHP-20P) to obtain (5R,6S,8R,2'S,4'S)-3-[(1-dimethylaminocarbonyl-2-acetoamidinomethylpyrrolidin)-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with 1 % tetrahydrofuran-water.

UV $\lambda_{max}^{H_2O}$ nm: 299.

IR ν_{max}^{KBr} cm^{-1}: 1756, 1590, 1500, 1395.

NMR δ (D_2O): 1.26 (3H, d, J = 6.3Hz), 2.20 (3H, s), 2.84 (3H, s), 2.85 (3H, s).

Example 10



(4R,5S,6S,8R,2'R,4'S)-3-[(2-Dimethylaminocarbonylmethylpyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid (15 mg) was dissolved in 15 ml of a morpholinopropanesulfonic acid buffer solution (pH 7.0). The mixture was cooled at 0°C and adjusted with 4N sodium hydroxide solution to pH 9.0, and 100 mg of benzyl formimidate hydrochloride was added thereto. The resulting mixture was kept at pH 9.0

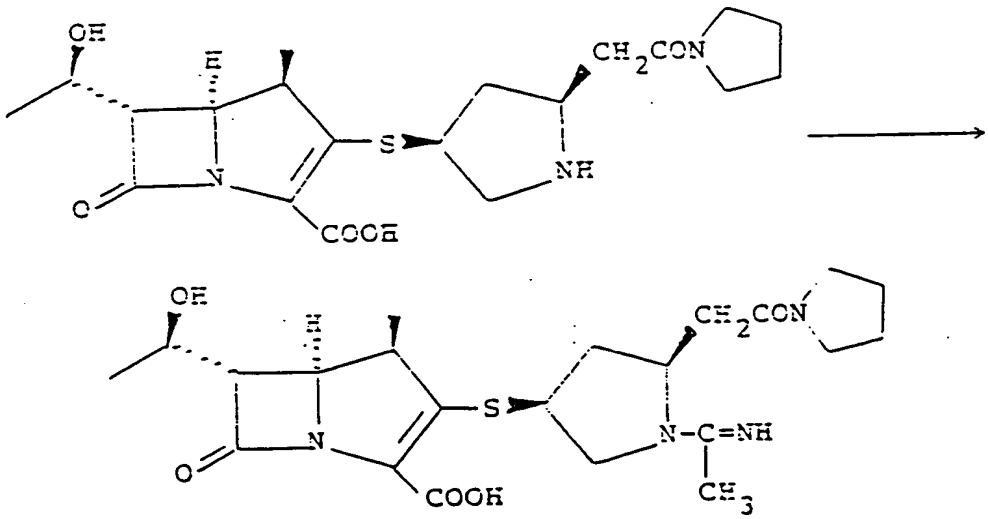
with 4N sodium hydroxide solution, followed by stirring for 10 minutes. The reaction solution was neutralized with 1N hydrochloric acid, washed with dichloromethane and distilled under reduced pressure to remove dichloromethane. The residual solution was subjected to polymer chromatography (CHP-20P) to obtain (4R,5S,6S,8R,2'R,4'S)-3-[(1-formimino-2-dimethylaminocarbonylmethylpyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with 1 % tetrahydrofuran-water.

UV $\lambda_{max}^{H_2O}$ nm: 298.

IR ν_{max}^{KBr} cm^{-1}: 1745, 1700, 1625, 1590, 1385.

NMR δ (D_2O): 1.21 (3H, d, J = 7.3Hz), 1.28 (3H, d, J = 6.6Hz), 2.93 (3H, s), 3.06 (3H, s), 7.99 (1H, s).

Example 11



(4R,5S,6S,8R,2'R,4'S)-3-[[2-(1-Pyrrolidine-carbonylmethyl)pyrrolidin]-4-ylthio]-4-methyl-6-(1-hydroxy-ethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid

(10 mg) was dissolved in a morpholinopropanesulfonic acid buffer solution. The mixture was cooled at 0°C and adjusted with 4N sodium hydroxide solution to pH 9.0, and 100 mg of ethyl acetoimidate hydrochloride was added in four portions thereto. The resultant mixture was adjusted with 4N sodium hydroxide solution to pH 9.0, followed by stirring for 2 hours. The reaction solution was subjected to polymer chromatography (CHP-20P) to obtain (4R,5S,6S,8R,2'R,4'S)-3-[(1-acetoimino-2-(1-pyrrolidinecarbonylmethyl)-pyrrolidin]-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-aza-bicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid from the fraction eluted with a 1 % tetrahydrofuran-water.

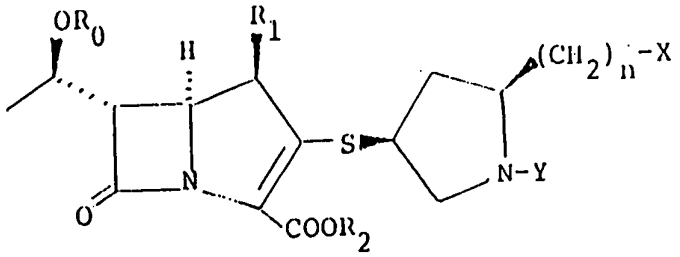
UV $\lambda_{max}^{H_2O}$ nm: 298.

IR ν_{max}^{KBr} cm^{-1}: 1750, 1685 (sh), 1610, 1450, 1380, 1255.

NMR δ (D_2O): 1.19 (3H, d, J = 7.3Hz), 1.28 (3H, d, J = 6.6Hz), 2.20 (3H, s).

According to the procedures as described in the preceding Examples, the compounds as shown in Tables 12, 13 and 14 were obtained.

Table 12



Example No.	R_0	R_1	R_2	X	Y	n	Physical data
12	H	Me	PNB	$CONH_2$	PNZ	1	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1690, 1520, 1400, 1345, 1105 NMR δ ($CDCl_3$): 1.28 (3H, d, J = 6.8Hz), 1.36 (3H, d, J = 7Hz), 5.22 (2H, s), 5.49 1H, d, J = 13.9Hz), 8.21 (4H, d, J = 8.8Hz)
	H	Me	H	$CONH_2$	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1750, 1665, 1590, 1487, 1280 NMR δ (D_2O): 1.20 (3H, d, J = 7.3Hz), 1.28 (3H, d, J = 6.3Hz), 3.44 (1H, dd, J = 2.6Hz and 6.3Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
13	PNZ	H	PNB	CON	PNZ	1	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1773, 1740, 1695, 1620, 1513, 1340, 1254 NMR δ ($CDCl_3$): 1.48 (3H, d, J = 6.2Hz), 5.22 (2H, s), 5.26 (2H, s), 5.46 (1H, d, J = 13.9Hz), 8.21 (6H, d, J = 6.3Hz)
	H	H	H	CON	H	1	UV $\nu_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1753, 1620, 1446, 1380 NMR δ (D_2O): 1.26 (3H, d, J = 6.3Hz)
14	H	Me	PNB	CON	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1765, 1700, 1620, 1520, 1347, 1210 NMR δ ($CDCl_3$): 1.27 (3H, d, J = 7.3Hz), 1.34 (3H, d, J = 6.4Hz), 5.22 (2H, s), 5.48 (1H, d, J = 13.9Hz), 8.40 (4H, d, J = 8.6Hz)
	H	Me	H	CON	H	1	UV $\nu_{max}^{H_2O}$ nm: 296 IR ν_{max}^{KBr} cm^{-1}: 1745, 1615, 1445, 1380 NMR δ (D_2O): 1.20 (3H, d, J = 7.3Hz), 1.27 (3H, d, J = 6.3Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
15	H	Me	PNB	COOMe	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1760, 1730 (sh), 1700, 1515, 1345, 1210 NMR δ ($CDCl_3$): 1.26 (3H, d, J = 7Hz), 1.34 (3H, d, J = 6.9Hz), 3.67 (3H, s), 5.22 (2H, s), 5.49 (1H, d, J = 13.6Hz), 8.20 (4H, d, J = 8.8Hz)
	H	Me	H	COOMe	H	1	UV $\lambda_{max}^{H_2O}$ nm: 296 IR ν_{max}^{KBr} cm^{-1}: 1755 (sh), 1735, 1600, 1385, 1260 NMR δ (D_2O): 1.20 (3H, d, J = 7Hz), 1.27 (3H, d, J = 6Hz), 3.44 (1H, dd, J = 2.3Hz and 6 Hz), 3.73 (3H, s), 4.19 (1H, d, J = 2.3Hz)
16	PNZ	H	PNB	$NHCONH_2$	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1782, 1750, 1700, 1608, 1520, 1350 NMR δ (DMSO-d_6): 5.35 (2H, s), 5.42 (2H, s), 8.33 (6H, d, J = 8.6Hz)
	H	H	H	$NHCONH_2$	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1750, 1652, 1585, 1383 NMR δ (D_2O): 1.27 (3H, d, J = 6.3Hz), 3.18 (2H, d, J = 9.2Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
17	PNZ	H	PNB	$NHCONMe_2$	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1780, 1742, 1692, 1636, 1520, 1255 NMR δ ($CDCl_3$): 1.50 (3H, d, J = 6.4Hz), 2.87 (6H, s), 5.26 (4H, s), 8.20 (6H, d J = 8.6Hz)
	H	H	H	$NHCONMe_2$	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1757, 1605 (sh), 1595, 1535, 1395 NMR δ (D_2O): 1.26 (3H, d, J = 6.4Hz), 2.88 (6H, s), 3.67 (2H, d, J = 9.2Hz)
18	PNZ	H	PNB	NHCOOEt	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1770, 1750, 1710, 1520, 1350, 1280 NMR δ ($CDCl_3$): 1.22 (3H, t, J = 7Hz), 1.48 (3H, d, J = 6.2Hz), 5.24 (4H, s), 8.20 (6H, d, J = 8.6Hz)
	H	H	H	NHCOOEt	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1746, 1700, 1585, 1380, 1245 NMR δ (D_2O): 3.17 (2H, d, J = 8.9Hz), 3.30 (1H, dd, J = 4.6Hz and 12.5Hz), 3.40 (1H, dd, J = 2.6Hz, and 5.9 Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
19	PNZ	H	PNB	$NHCOCH_3$	PNZ	1	IR $\overset{neat}{max}$ cm^{-1}: 1780, 1745, 1695, 1520, 1347, 1256 NMR δ ($CDCl_3$): 1.48 (3H, d, J = 6.2Hz), 1.95 (3H, s), 5.25 (4H, s)
	H	H	H	$NHCOCH_3$	H	1	UV $\overset{H_2O}{max}$ nm: 298 IR $\overset{KBr}{max}$ cm^{-1}: 1750, 1650, 1593, 1385, 1195, 1040 NMR δ (D_2O): 1.28 (3H, d, J = 6Hz), 2.03 (3H, s), 3.19 (2H, d, J = 9.2Hz)
20	PNZ	H	PNB	$OCONH_2$	PNZ	1	IR $\overset{neat}{max}$ cm^{-1}: 1703, 1740, 1705, 1525, 1348, 1260 NMR δ ($CDCl_3$): 1.48 (3H, d, J = 6.2Hz), 5.22 (4H, s), 5.46 (1H, d, J = 13.9Hz)
	H	H	H	$OCONH_2$	H	1	UV $\overset{H_2O}{max}$ nm: 298 IR $\overset{KBr}{max}$ cm^{-1}: 1725, 1595, 1395, 1520, 1092 NMR δ (D_2O): 1.26 (3H, d, J = 6.3Hz), 3.40 (1H, dd, J = 2.6Hz and 5.9Hz), 3.57 (1H, dd, J = 6.9Hz, and 12.2Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
21	PNZ	H	PNZ	$OCONMe_2$	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1773, 1740, 1700, 1515, 1340, 1253 NMR δ ($CDCl_3$): 1.49 (3H, d, J = 6.4Hz), 2.88 (6H, s), 5.23 (4H, s), 5.46 (1H, d, J = 13.6Hz), 8.20 (6H, d, J = 8.4Hz)
	H	H	H	$OCONMe_2$	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1755, 1690, 1592, 1385, 1193 NMR δ (D_2O): 1.27 (3H, d, J = 6.3Hz), 2.89 (3H, s), 2.94 (3H, s), 3.40 (1H, dd, J = 2.6Hz and 5.9Hz), 3.56 (1H, dd, J = 6.9Hz and 12.2Hz)
22	PNZ	H	PNB	NHPNZ	$CONMe_2$	1	IR ν_{max}^{neat} cm^{-1}: 1780, 1740(sh), 1720, 1625(sh), 1610, 1514 NMR δ ($CDCl_3$): 1.49 (3H, d, J = 6.4Hz), 2.83 (6H, s), 5.18 (2H, s), 5.26 (2H, s)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
23	PNZ	H	PNB	OCONHMe	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1773, 1745 (sh), 1702, 1520, 1343, 1260 NMR δ ($CDCl_3$): 1.48 (3H, d, J = 6.4Hz), 2.95 (3H, s), 5.25 (4H, s),
	H	H	H	OCONHMe	H	1	UV $\lambda_{max}^{H_2O}$ nm: 296 IR ν_{max}^{KBr} cm^{-1}: 1758, 1712, 1508, 1385, 1255, 1140 NMR δ (D_2O): 1.27 (3H, d, J = 6.6Hz), 2.71 (3H, s), 3.41 (1H, dd, J = 2.6Hz and 5.9Hz),
24	PNZ	H	PNB	OCOOEt	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1770, 1740, 1708, 1515, 1340 NMR δ ($CDCl_3$): 1.31 (3H, t, J = 7Hz), 1.49 (3H, d, J = 6.2Hz), 4.19 (2H, q, J = 7Hz), 5.24 (4H, s), 5.47 (1H, d, J = 14.1Hz), 8.20 (6H, d, J = 8.6Hz)
	H	H	H	OCOOEt	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1747, 1600, 1386, 1260 NMR δ (D_2O): 1.26 (3H, d, J = 6.6Hz), 1.28 (3H, t, J = 6.9Hz), 3.30 (1H, dd, J = 5.6Hz and 12.2 Hz), 3.40 (1H, dd J=2.6 Hz and 5.9Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
25	PNZ	H	PNB	$OCOCH_3$	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1772, 1730, 1698, 1517, 1342, 1225 NMR δ ($CDCl_3$): 1.49 (3H, d, J = 6.4Hz), 2.06 (3H, s), 5.24 (4H, s), 5.47 (1H, d, J = 13.6Hz), 8.20 (6H, d, J = 8.4Hz)
	H	H	H	$OCOCH_3$	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm-1: 1740, 1590, 1385, 1230 NMR δ (D_2O): 1.26 (3H, d, J = 6.3Hz), 2.14 (3H, s)
26	PNZ	H	PNB	$CONH_2$	PNZ	2	IR ν_{max}^{Nujol} cm^{-1}: 1790, 1746, 1708, 1660, 1600, 1510 NMR δ ($CDCl_3$): 1.34 (3H, d, J = 6.1Hz), 5.22 (2H, s), 5.30 (2H, s), 8.21 (6H, d, J = 8.6Hz)
	H	H	H	$CONH_2$	H	2	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1750, 1660, 1585, 1387 NMR δ (D_2O): 1.25 (3H, d, J = 6.6Hz), 2.39 (2H, t, J = 7.7Hz), 3.27 (1H, dd, J = 5.2Hz and 12.5Hz), 3.38 (1H, dd, J = 2.6Hz and 5.9Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
27	H	Me	PNB	$CONH_2$	PNZ	2	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1770, 1520, 1347, 1102 NMR δ (acetone-d_6): 1.27 (6H, d, J = 6.2Hz), 5.25 (2H, s), 5.51 (1H, d, J = 14.1Hz)
	H	Me	H	$CONH_2$	H	2	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1750, 1663, 1590, 1383, 1246 NMR δ (D_2O): 1.18 (3H, d, J = 7.3Hz) 1.26 (3H, d, J = 6.6Hz), 3.43 (1H, dd, J = 2.6Hz and 6.3Hz)
28	PNZ	H	PNB	CON(H)Me	PNZ	2	IR ν_{max}^{Nujol} cm^{-1}: 1788, 1742, 1704, 1633, 1512 NMR δ (DMSO-d_6): 3.22 (3H, s), 5.22 (2H, s), 5.30 (2H, s), 8.21 (6H, d, J = 8.6Hz)
	H	H	H	CON(H)Me	H	2	UV $\lambda_{max}^{H_2O}$ nm: 299 IR ν_{max}^{KBr} cm^{-1}: 1757, 1638, 1590, 1380, 1240 NMR δ (D_2O): 1.25 (3H, d, J = 6.3Hz), 2.69 (3H, s), 3.38 (1H, dd, J = 2.6Hz and 6.3Hz)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
29	PNZ	H	PNB	$CONMe_2$	PNZ	2	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1782, 1750, 1700, 1638, 1523 NMR δ ($CDCl_3$): 1.48 (3H, d, J = 6.4Hz), 2.91 (3H, s), 2.94 (3H, s), 5.26 (2H, s), 5.21 (2H, s), 5.48 (1H, d, J = 13.9Hz), 8.20 (6H, d, J = 8.6Hz)
	H	H	H	$CONMe_2$	H	2	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1750, 1620, 1590, 1385, 1245 NMR δ (D_2O): 1.25 (3H, d, J = 6.3Hz) 2.90 (3H, s), 3.03 (3H, s)
30	PNZ	H	PNB	OH	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1778, 1748, 1700, 1515, 1305, 1259 NMR δ ($CDCl_3$): 1.48 (3H, d, J = 6.4Hz), 5.23 (4H, s), 5.46 (1H, d, J = 13.9Hz), 8.20 (6H, d, J = 8.6Hz)
	H	H	H	OH	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1750, 1585, 1385, 1240 NMR δ (D_2O): 1.26 (3H, d, J = 6.3Hz), 3.18 (2H, d, J = 8.9Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
31	H	Me	H	OH	CH=NH	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1742, 1698, 1582, 1380 NMR δ (D_2O): 1.19 (3H, d, J = 7.3Hz), 1.27 (3H, d, J = 6.3Hz), 8.05 (1H, s)
32	H	Me	H	OH	$C(CH_3)=NH$	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1740, 1693, 1605, 1382 NMR δ (D_2O): 1.19 (3H, d, J = 6.9Hz), 1.27 (3H, d, J = 6.3Hz), 2.20 (3H, s)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
33	PNZ	H	PNB	SMe	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1778, 1730, 1705, 1520, 1345, 1260 NMR δ ($CDCl_3$): 1.49 (3H, d, J = 6.4Hz), 2.09 (3H, s), 5.23 (2H, s), 5.25 (2H, s), 5.47 (1H, d, J = 13.6Hz), 8.20 (6H, d, J = 8.6Hz)
	H	H	H	SMe	H	1	UV $\lambda_{max}^{H_2O}$ nm: 297 IR ν_{max}^{KBr} cm^{-1}: 1755, 1590, 1380, 1238 NMR δ (D_2O): 1.26 (3H, d, J = 6.3Hz), 2.14 (3H, s), 3.17 (2H, d, J = 8.9Hz)
34	PNZ	H	PNB	SO_2Me	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1780, 1750, 1703, 1520, 1308, 1263 NMR δ ($CDCl_3$): 1.49 (3H, d, J = 6.4Hz), 2.75 (3/2H, s), 2.80 (3/2H, s), 5.23 (2H, s), 5.25 (2H, s), 5.47 (1H, d, J = 13.9 Hz), 8.20 (6H, d, J = 8.8Hz)
	H	H	H	SO_2	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1755, 1590, 1390, 1292, 1128 NMR δ (D_2O): 1.26 (3H, d, J = 6.3Hz), 3.15 (3H, s), 3.39 (1H, dd, J = 2.3Hz and 5.9Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
35	PNZ	H	PNB	OMe	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1783, 1752, 1708, 1528, 1350 NMR δ ($CDCl_3$): 1.49 (3H, d, J = 6.4Hz), 3.33 (3H, s), 5.23 (2H, s), 5.25 (2H, s), 5.47 (1H, d, J = 13.9Hz), 8.20 (6H, d, J = 8.6Hz)
	H	H	H	OMe	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1752, 1590, 1382, 1242 NMR δ (D_2O): 1.26 (3H, d, J = 6.6Hz), 3.40 (3H, s)
36	H	Me	PNB	CN	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 2250, 1770, 1705, 1513, 1350 NMR δ ($CDCl_3$): 1.28 (3H, d, J = 7Hz), 1.35 (3H, d, J = 6Hz), 5.23 (2H, s), 5.48 (1H, d, J = 13.9Hz), 8.21 (4H, d, J = 8.1Hz)
	H	Me	H	CN	H	1	UV $\lambda_{max}^{H_2O}$ nm: 300 IR ν_{max}^{KBr} cm^{-1}: 2250, 1750, 1593, 1390 NMR δ (D_2O): 1.21 (3H, d, J = 7.3Hz), 1.29 (3H, d, J = 6.3Hz), 3.16 (1H, dd, J = 4.3Hz and 12.2Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
37	PNZ	H	PNB	CN	PNZ	1	IR_{max}^{neat} cm^{-1}: 2245, 1770, 1745, 1700, 1519 NMR ($CDCl_3$): 1.48 (3H, d, J = 6.2Hz), 5.24 (4H, s), 8.18 (6H, d, J = 8.8 Hz)
	H	H	H	CN	H	1	$UV_{max}^{H_2O}$ nm: 298 IR_{max}^{KBr} cm^{-1}: 1750, 1585, 1383 NMR δ (D_2O): 1.28 (3H, d, J = 6.6Hz), 3.72 (1H, dd, J = 7.6Hz and 12.5Hz)
38	H	Me	PNB	OMe	PNZ	1	IR_{max}^{neat} cm^{-1}: 1765, 1700, 1520, 1340 NMR δ ($CDCl_3$): 1.27 (3H, d, J = 6.6Hz), 1.48 (3H, d, J = 6.2Hz), 3.33 (3H, s), 5.22 (2H, s), 5.48 (1H, d, J = 13.6Hz), 8.20 (4H, d, J=8.4 HZ)
	H	Me	H	OMe	H	1	$UV_{max}^{H_2O}$ nm: 298 IR_{max}^{KBr} cm^{-1}: 1753, 1597, 1385 NMR δ (D_2O): 1.19 (3H, d, J = 7.3Hz), 1.26 (3H, d, J = 6.3Hz), 3.39 (3H, s), 3.44 (1H, dd, J = 2.4Hz and 6.3Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
39	H	Me	PNB	CON(H)Me	PNZ	3	IR ν_{max}^{neat} cm^{-1}: 1775, 1705, 1658, 1525, 1348 NMR δ ($CDCl_3$): 1.26 (3H, d, J = 7Hz), 1.34 (3H, d, J = 6.4Hz), 2.77 (3H, d, J = 4.8Hz), 5.20 (2H, s), 5.47 (1H, d, J = 13.6 Hz)
	H	Me	H	CON(H)Me	H	3	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1752, 1640, 1590, 1383 NMR δ (D_2O): 1.20 (3H, d, J = 7.3Hz), 1.27 (3H, d, J = 6.3Hz), 2.29 (2H, t, J = 7Hz), 2.71 (3H, s)
40	H	Me	PNB	CON(H)Me	PNZ	4	IR ν_{max}^{neat} cm^{-1}: 1763, 1700, 1655, 1520, 1343 NMR δ ($CDCl_3$): 1.27 (3H, d, J = 7Hz), 1.35 (3H, d, J = 7Hz), 2.78 (3H, d, J = 4.8Hz), 5.21 (2H, s), 8.21 (4H, d, J = 8.8Hz)
	H	Me	H	CON(H)Me	H	4	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1752, 1640, 1590, 1385 NMR δ (D_2O): 1.22 (3H, d, J = 6.9Hz), 1.30 (3H, d, J = 6.3Hz), 2.27 (2H, t, J = 7Hz), 2.73 (3H, s)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
41	H	Me	PNB	COOPNB	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1762, 1736, 1703, 1519, 1342 NMR δ ($CDCl_3$): 1.26 (3H, d, J = 6.8Hz), 1.34 (3H, d, J = 6.2Hz), 5.20 (4H, s), 8.19 (6H, d, J = 8.8Hz)
	H	Me	H	COOH	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1750, 1598, 1393, 1180 NMR δ (D_2O): 1.22 (3H, d, J = 7.3Hz), 1.30 (3H, d, J = 6.3Hz), 3.47 (1H, dd, J = 2.6Hz and 6.3Hz)
42	H	Me	PNB	COOPNB	PNZ	2	IR ν_{max}^{neat} cm^{-1}: 1770, 1730, 1693, 1604, 1515 NMR δ ($CDCl_3$): 1.26 (3H, d, J = 7.3Hz), 1.34 (3H, d, J = 6Hz), 5.20 (4H, S), 8.18 (6H, d, J = 8.1Hz)
	H	Me	H	COOH	H	2	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1755, 1608, 1570, 1400 NMR δ (D_2O): 1.23 (3H, d, J = 7.3Hz), 1.30 (3H, d, J = 6.6Hz)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
43	H	Me	PNB	CH=N-OMe	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1760, 1700, 1520, 1400, 1345 NMR δ ($CDCl_3$): 1.27 (3H, d, J = 6.8Hz), 1.35 (3H, d, J = 5.9Hz), 5.23 (2H, s), 5.49 (1H, d, J = 13.9Hz), 8.20 (4H, d, J = 8.6Hz)
	H	Me	H	CH=N-OMe	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1750, 1595, 1390 NMR δ (D_2O): 1.22 (3H, d, J = 7.3Hz), 1.29 (3H, d, J = 6.3Hz), 3.47 (1H, dd, J = 2.6Hz and 5.9Hz), 3.85, 3.90 (3H, s)

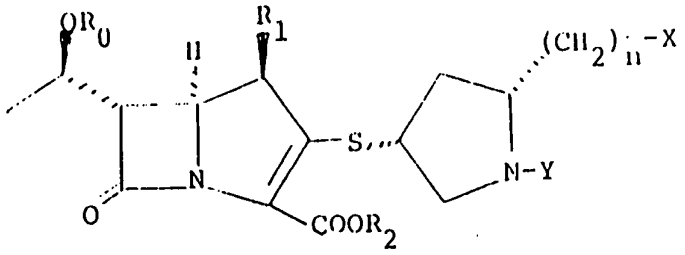
(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
44	H	Me	PNB	CH=N-NMe_2	PNZ	1	IR_{max}^{neat} cm^{-1}: 1765, 1700, 1520, 1400, 1340 NMR δ ($CDCl_3$): 1.19 (3H, d, J = 7Hz), 1.27 (3H, d, J = 7Hz), 2.73 (6H, S), 5.23 (2H, s), 8.21 (4H, d, J = 8.8Hz)
	H	Me	H	CH=N-NMe_2	H	1	$UV_{max}^{H_2O}$ nm: 238, 298 IR_{max}^{KBr} cm^{-1}: 1748, 1590, 1383 NMR δ (D_2O): 1.22 (3H, d, J = 7.3Hz), 1.30 (3H, d, J = 6.6Hz), 2.72 (6H, s), 3.47 (1H, dd, J = 2.6Hz and 6.3 Hz), 6.02 (1H, t, J = 5Hz)
45	H	Me	PNB	CONHNMe_2	PNZ	1	IR_{max}^{neat} cm^{-1}: 1763, 1700, 1520, 1400, 1342 NMR δ ($CDCl_3$): 1.28 (3H, d, J = 7Hz), 1.35 (3H, d, J = 6.4Hz), 2.49 (3H, s), 2.56 (3H, s), 5.22 (2H, s), 8.21 (4H, d, J = 8.4Hz)
	H	Me	H	CONHNMe_2	H	1	$UV_{max}^{H_2O}$ nm: 296 IR_{max}^{KBr} cm^{-1}: 1745, 1650, 1590, 1383 NMR δ (D_2O): 1.22 (3H, d, J = 7.3Hz), 1.30 (3H, d, J = 6.6Hz), 2.55 (6H, s)

(Continued)

Example No.	R_0	R_1	R_2	X	Y	n	Physical data
46	H	Me	PNB	OH	PNZ	2	IR_{max}^{neat} cm^{-1}: 1768, 1690, 1520, 1348, 1212 NMR δ ($CDCl_3$): 1.28 (3H, d, J = 7.3Hz), 1.35 3H, d, J = 6.3Hz), 5.23 (2H, s), 5.50 (1H, d, J = 13.9Hz)
	H	Me	H	OH	H	2	$UV_{max}^{H_2O}$ nm: 298 IR_{max}^{KBr} cm^{-1}: 1750, 1588, 1383 NMR δ (D_2O): 1.23 (3H, d, J = 7.3Hz), 1.30 (3H, d, J = 6.3Hz), 3.47 (1H, dd, J = 2.6Hz and 6.3 Hz)
47	H	Me	PNB	OH	PNZ	3	IR_{max}^{neat} cm^{-1}: 1770, 1690, 1520, 1348, 1208 NMR δ ($CDCl_3$): 1.28 (3H, d, J = 7Hz), 1.36 (3H, d, J = 6.3Hz), 5.50 (1H, d, J = 13.5Hz), 7.65 (2H, d, J = 8.9Hz)
	H	Me	H	OH	H	3	$UV_{max}^{H_2O}$ nm: 298 IR_{max}^{KBr} cm^{-1}: 1752, 1595, 1388 NMR δ (D_2O): 1.22 (3H, d, J = 7.3Hz), 1.30 (3H, d, J = 6.3Hz)

Table 13

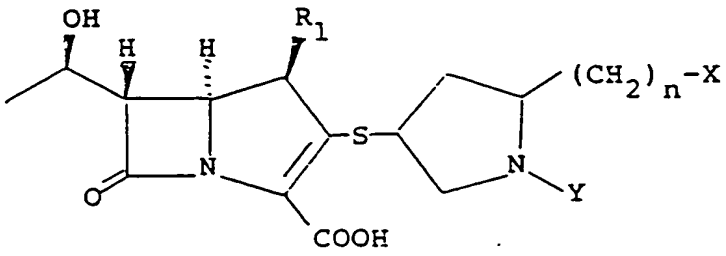


Example No.	R_0	R_1	R_2	X	Y	n	Physical data
48	H	Me	PNB	OH	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1760, 1685, 1512, 1340 NMR δ ($CDCl_3$): 1.27 (3H, d, J = 7.3Hz), 1.34 (3H, d, J=6.3 Hz), 5.24 (2H, s), 5.48 (1H, d, J = 13.9Hz) 7.52 (2H, d, J = 8.9Hz), 7.63 (2H d, J=8.9 Hz)
	H	Me	H	OH	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1752, 1598, 1395 NMR δ (D_2O): 1.22 (3H, d, J=7.3 Hz), 1.30 (3H, d, J=6.3 Hz) 3.48 (1H, dd, J=2.6 Hz and 5.9 Hz)

(Continued)

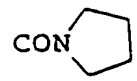
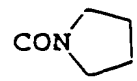
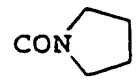
Example No.	R_0	R_1	R_2	X	Y	n	Physical data
49	H	Me	PNB	CON(Me)(Me)	PNZ	1	IR ν_{max}^{neat} cm^{-1}: 1760, 1705, 1660, 1524 NMR δ ($CDCl_3$): 1.27 (3H, d, J=7.3 Hz), 1.36 (3H, d, J=6.3 Hz), 2.72 (3H, d, J=4.6 Hz), 5.22 (2H, s), 5.50 (1H, d, J=13.5 Hz), 7.52 (2H, d, J=8.3 Hz), 7.66 (2H d, J=8.6 Hz)
	H	Me	H	CON(Me)(Me)	H	1	UV $\lambda_{max}^{H_2O}$ nm: 298 IR ν_{max}^{KBr} cm^{-1}: 1745, 1642, 1580, 1380 NMR δ (D_2O): 1.22 (3H, d, J=7.3 Hz), 1.31 (3H, d, J=6.3 Hz), 2.74 (3H, s)

Table 14

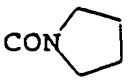


No.	R_1	n	X	Y
1	H	1	$CONH_2$	H
2	Me	1	$CONH_2$	H
3	H	1	CONHMe	H
4	Me	1	CONHMe	H
5	H	1	$CONMe_2$	H
6	Me	1	$CONMe_2$	H
7	H	1	CON⟨pyrrolidine⟩	H
8	Me	1	CON⟨pyrrolidine⟩	H
9	H	1	CON⟨azetidine⟩	H
10	Me	1	CON⟨azetidine⟩	H
11	H	1	CON⟨piperidine⟩	H
12	Me	1	CON⟨piperidine⟩	H
13	H	1	COOMe	H
14	Me	1	COOMe	H
15	H	1	COOEt	H
16	Me	1	COOEt	H

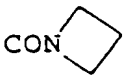
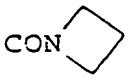
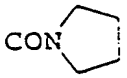
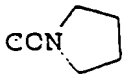
(Continued)

No.	R_1	n	X	Y
40	Me	1	NH-C(Me)=NH	$CONMe_2$
41	H	1	$CONH_2$	CH=NH
42	Me	1	$CONH_2$	CH=NH
43	H	1	$CONH_2$	C(Me)=NH
44	Me	1	$CONH_2$	C(Me)=NH
45	H	1	CONHMe	CH=NH
46	Me	1	CONHMe	CH=NH
47	H	1	CONHMe	C(Me)=NH
48	Me	1	CONHMe	C(Me)=NH
49	H	1	$CONMe_2$	CH=NH
50	Me	1	$CONMe_2$	CH=NH
51	H	1	$CONMe_2$	C(Me)=NH
52	Me	1	$CONMe_2$	C(Me)=NH
53	H	1		CH=NH
54	Me	1		CH=NH
55	H	1		C(Me)=NH

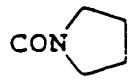
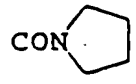
(Continued)

No.	R_1	n	X	Y
56	Me	1		C(=NH)Me
57	H	1	$NHCONMe_2$	CH=NH
58	Me	1	$NHCONMe_2$	CH=NH
59	H	1	$NHCONMe_2$	C(=NH)Me
60	Me	1	$NHCONMe_2$	C(=NH)Me
61	H	1	CONHEt	H
62	Me	1	CONEt	H
63	H	1	$CONEt_2$	H
64	Me	1	$CONEt_2$	H
65	H	1	NHCONHEt	H
66	Me	1	NHCONHEt	H
67	H	1	$NHCONEt_2$	H
68	Me	1	$NHCONEt_2$	H
69	H	1	OCONHEt	H
70	Me	1	OCONHEt	H
71	H	1	$OCONEt_2$	H
72	Me	1	$COEt_2$	H
73	H	1	OCOEt	H
74	Me	1	OCOEt	H
75	H	1	OCOOMe	H
76	Me	1	OCOOMe	H

(Continued)

No.	R_1	n	X	Y
77	H	1	OCOOEt	H
78	Me	1	OCOOEt	H
79	H	1	COOH	H
80	Me	1	COOH	H
81	H	2	$CONH_2$	H
82	Me	2	$CONH_2$	H
83	H	2	CONHMe	H
84	Me	2	CONHMe	H
85	H	2	$CONMe_2$	H
86	Me	2	$CONMe_2$	H
87	H	2		H
88	Me	2		H
89	H	2		H
90	Me	2		H
91	H	2	COOMe	H
92	Me	2	COOMe	H
93	H	2	COOH	H
94	Me	2	COOH	H
95	H	2	$CONH_2$	CH=NH
96	Me	2	$CONH_2$	CH=NH
97	H	2	$CONH_2$	C(=NH)Me

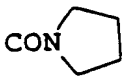
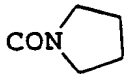
(Continued)

No.	R_1	n	X	Y
98	Me	2	$CONH_2$	C(=NH)(Me)
99	H	2	CONHMe	CH=NH
100	Me	2	CONHMe	CH=NH
101	H	2	CONHMe	C(=NH)(Me)
102	Me	2	CONHMe	C(=NH)(Me)
103	H	2	$CONMe_2$	CH=NH
104	Me	2	$CONMe_2$	CH=NH
105	H	2	$CONMe_2$	C(=NH)(Me)
106	Me	2	$CONMe_2$	C(=NH)(Me)
107	H	3	$CONH_2$	H
108	Me	3	$CONH_2$	H
109	H	3	CONHMe	H
110	Me	3	CONHMe	H
111	H	3	$CONMe_2$	H
112	Me	3	$CONMe_2$	H
113	H	3		H
114	Me	3		H
115	H	3	COOMe	H
116	Me	3	COOMe	H

(Continued)

No.	R_1	n	X	Y
117	H	3	COOH	H
118	Me	3	COOH	H
119	H	3	$CONH_2$	CH=NH
120	Me	3	$CONH_2$	CH=NH
121	H	3	$CONH_2$	C(=NH)Me
122	Me	3	$CONH_2$	C(=NH)Me
123	H	3	CONHMe	CH=NH
124	Me	3	CONHMe	CH=NH
125	H	3	CONHMe	C(=NH)Me
126	Me	3	CONHMe	C(=NH)Me
127	H	3	$CONMe_2$	CH=NH
128	Me	3	$CONMe_2$	CH=NH
129	H	3	$CONMe_2$	C(=NH)Me
130	Me	3	$CONMe_2$	C(=NH)Me
131	H	4	$CONH_2$	H
132	Me	4	$CONH_2$	H
133	H	4	CONHMe	H
134	Me	4	CONHMe	H
135	H	4	$CONMe_2$	H

(Continued)

No.	R_1	n	X	Y
136	Me	4	$CONMe_2$	H
137	H	4	COOMe	H
138	Me	4	COOMe	H
139	H	4	COOH	H
140	Me	4	COOH	H
141	H	4		H
142	Me	4		H
143	H	4	$CONH_2$	CH=NH
144	Me	4	$CONH_2$	CH=NH
145	H	4	$CONH_2$	C(=NH)Me
146	Me	4	$CONH_2$	C(=NH)Me
147	H	4	CONHMe	CH=NH
148	Me	4	CONHMe	CH=NH
149	H	4	CONHMe	C(=NH)Me
150	Me	4	CONHMe	C(=NH)Me
151	H	4	$CONMe_2$	CH=NH
152	Me	4	$CONMe_2$	CH=NH
153	H	4	$CONMe_2$	C(=NH)Me

(Continued)

No.	R_1	n	X	Y
154	Me	4	$CONMe_2$	C=NH | Me
155	H	1	CN	H
156	Me	1	CN	H
157	H	1	CH=N-OMe	H
158	Me	1	CH=N-OMe	H
159	H	1	CH=N-OEt	H
160	Me	1	CH=N-OEt	H
161	H	1	$CH=NNMe_2$	H
162	Me	1	$CH=NNMe_2$	H
163	H	1	$CH=NNEt_2$	H
164	Me	1	CH=NNEt	H
165	H	1	CH=NN(Me)(Et)	H
166	Me	1	CH=NN(Me)(Et)	H
167	H	1	CH=NNHMe	H
168	Me	1	CH=NNHMe	H
169	H	1	$CONHNH_2$	H
170	Me	1	$CONHNH_2$	H
171	H	1	$CONHNMe_2$	H
172	Me	1	$CONHNMe_2$	H
173	H	1	$CONMeNMe_2$	H
174	Me	1	$CONMeNMe_2$	H
175	H	1	$CONHNEt_2$	H

(Continued)

No.	R_1	n	X	Y
176	Me	1	$CONHNEt_2$	H
177	H	1	$CONMeNEt_2$	H
178	Me	1	$CONMeNEt_2$	H
179	H	1	$CONMeN(Me)(Et)$	H
180	Me	1	$CONMeN(Me)(Et)$	H
181	H	1	OH	H
182	Me	1	OH	H
183	H	1	SMe	H
184	Me	1	SMe	H
185	H	1	SEt	H
186	Me	1	SEt	H
187	H	1	S(n)Pr	H
188	Me	1	S(n)Pr	H
189	H	1	S(i)Pr	H
190	Me	1	S(i)Pr	H
191	H	1	SO_2Me	H
192	Me	1	SO_2Me	H
193	H	1	SO_2Et	H
194	Me	1	SO_2Et	H
195	H	1	SO_2(n)Pr	H
196	Me	1	SO_2(n)Pr	H
197	H	1	SO_2(i)Pr	H
198	Me	1	SO_2(i)Pr	H

(Continued)

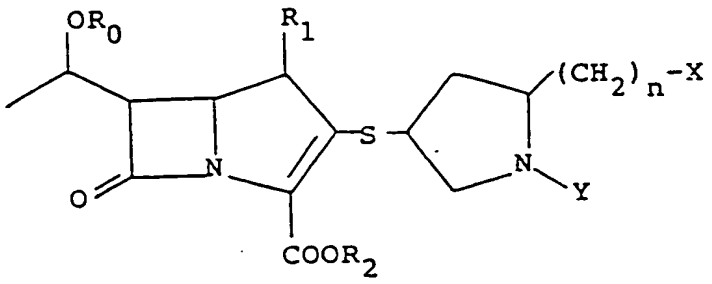
No.	R_1	n	X	Y
199	H	1	OMe	H
200	Me	1	OMe	H
201	H	1	OEt	H
202	Me	1	OEt	H
203	H	1	O(n)Pr	H
204	Me	1	O(n)Pr	H
205	H	1	O(i)Pr	H
206	Me	1	O(i)Pr	H
207	H	1	OH	CH=NH
208	Me	1	OH	CH=NH
209	H	1	OH	C(=NH)Me
210	Me	1	OH	C(=NH)Me
211	H	1	SMe	CH=NH
212	Me	1	SMe	CH=NH
213	H	1	SMe	C(=NH)Me
214	Me	1	SMe	C(=NH)Me
215	H	1	SO_2Me	CH=NH
216	Me	1	SO_2Me	CH=NH
217	H	1	SO_2Me	C(=NH)Me

(Continued)

No.	R_1	n	X	Y
218	Me	1	SO_2Me	C=NH | Me
219	H	1	OMe	CH=NH
220	Me	1	OMe	CH=NH
221	H	1	OMe	C=NH | Me
222	Me	1	OMe	C=NH | Me

What is claimed is:

1. A compound of the formula:



(I)

wherein R_1 is a hydrogen atom or a lower alkyl group, R_2 is a hydrogen atom or a conventional protecting group for a carboxyl group, R_0 is a hydrogen atom or a conventional protecting group for a hydroxyl group, X is a protected or unprotected amino group, a carboxyl group, a lower alkoxycarbonyl group, an ar(lower)alkyloxycarbonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower alkylthio group, a lower alkylsulfonyl group or a group of either one of the following formulas:

(1) $-CON\begin{matrix}R_3\\R_4\end{matrix}$

wherein R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, or they are taken together to represent an alkylene chain to form, in combination with the adjacent nitrogen atom, a 3- to 7-membered cyclic amino group,

(2) $-ZCOR_5$

wherein Z represents -NH- or -O- and R_5 represents an amino group, a mono(lower)alkylamino group, a di(lower)alkylamino group, a lower alkyloxy group or a lower alkyl group,

(3) $-NH-\underset{\underset{R_6}{|}}{C}=NH$

wherein R_6 represents a hydrogen atom or a lower alkyl group,

(4) $-CH=N-R_7$

wherein R_7 represents a mono(lower)alkylamino group, a di-(lower)alkylamino group or a lower alkyloxy group, or

(5) $-CO-\underset{\underset{R_8}{|}}{N}-N\begin{matrix}\nearrow R_9\\ \searrow R_{10}\end{matrix}$

wherein R_8, R_9 and R_{10}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, Y represents a hydrogen atom, a conventinal protecting group for an amino group or a group of either one of the following formulas:

(6) $-CON\begin{matrix}\nearrow R_{11}\\ \searrow R_{12}\end{matrix}$

wherein R_{11} and R_{12}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group or

(7) $-\underset{\underset{R_6}{|}}{C}=NH$

wherein R_6 is as defined above and n is an integer of 1 to 6, and a pharmacologically acceptable salt thereof.

2. A compound as claimed in Claim 1, wherein R_0 and R_2 each is a hydrogen atom and X is an amino group, a carboxyl group, a lower alkoxycarbonyl group, an ar(lower)-alkyloxycarbonyl group, a cyano group, a hydroxyl group, a

lower alkyloxy group, a lower alkylthio group, a lower alkylsulfonyl group or a group of either one of the following formulas:

(1) $-CON\begin{matrix}R_3\\R_4\end{matrix}$

wherein R_3 and R_4 are as defined in Claim 1,

(2) $-ZCOR_5$

wherein Z and R_5 are as defined in Claim 1,

(3) $-NH-\underset{\displaystyle R_6}{\overset{\displaystyle |}{C}}=NH$

wherein R_6 is as defined in Claim 1,

(4) $-CH=N-R_7$

wherein R_7 is as defined in Claim 1, or

(5) $-CON(R_8)-N\begin{matrix}R_9\\R_{10}\end{matrix}$

wherein R_8, R_9 and R_{10} are as defined in Claim 1, and Y is a hydrogen atom or a group of either one of the following formulas:

(6) $-CON\begin{matrix}R_{11}\\R_{12}\end{matrix}$

wherein R_{11} and R_{12} are as defined in Claim 1, or

(7) $-\underset{\displaystyle R_6}{\overset{\displaystyle |}{C}}=NH$

wherein R_6 is as defined in Claim 1.

3. A compound as claimed in Claim 1, wherein R_0 and R_2 each is a hydrogen atom, X is a carboxyl group, a

lower alkoxycarbonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group or a group of either one of the following formulas:

(1) $-CON\begin{matrix}R_3\\R_4\end{matrix}$

wherein R_3 and R_4 are as defined in Claim 1,

(4) $-CH=N-R_7$

wherein R_7 is as defined in Claim 1, or

(5) $-CON(R_8)-N\begin{matrix}R_9\\R_{10}\end{matrix}$

wherein R_8, R_9 and R_{10} are as defomed om Claim 1, and Y is a hydrogen atom.

4. A compound as claimed in Claim 3, wherein X is a group of the formula:

$-CON\begin{matrix}R_{3a}\\R_{4a}\end{matrix}$

wherein R_{3a} and R_{4a} each represents a hydrogen atom or a methyl group.

5. A compound as claimed in Claim 3, wherein X is a hydroxyl group or a lower alkyloxy group.

6. A compound as claimed in any one of claims 1 to 5, wherein R_1 is a methyl group.

7. A compound as claimed in Claim 6, which has a

(5S)-configuration.

8. A compound as claimed in Claim 7, which has a (4R,5S,6S,8R)-configuration.

9. A compound as claimed in Claim 3, wherein R_1 is a hydrogen atom.

10. A compound as claimed in Claim 9, which has a (5R)-configuration.

11. A compound as claimed in Claim 10, which has a (5R,6S,8R)-configuration.

12. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'R,4'S)-3-[(2-dimethylaminocarbonylmethyl-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-aza-bicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

13. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'R,4'S)-3-[(2-methylaminocarbonylmethyl-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-aza-bicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

14. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'R,4'S)-3-[(2-carbamoylmethylpyrrolidin)-4-

ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

15. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'R,4'S)-3-[(2-(2-dimethylaminocarbonylethyl)-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-aza-bicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

16. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'R,4'S)-3-[(2-(2-methylaminocarbonylethyl)-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-aza-bicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

17. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'R,4'S)-3-[(2-(2-carbamoylethyl)pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

18. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'S,4'S)-3-[(2-hydroxymethylpyrrolidin)-4-yl-thio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

19. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'S,4'S)-3-[2-methoxymethylpyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-

hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

20. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'R,4'S)-3-[(2-(2-carboxyethyl)pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo-[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

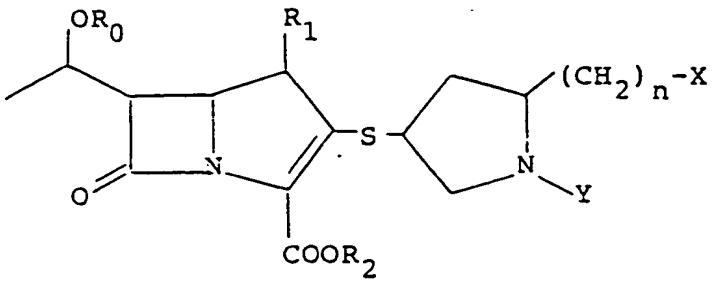
21. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'R,4'S)-3-[(2-methoxycarbonylmethyl-pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-aza-bicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

22. A compound as claimed in Claim 1, which is (4R,5S,6S,8R,2'R,4'S)-3-[(2-(2-N,N-dimethylhydrazono-ethyl)pyrrolidin)-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylic acid, or a salt thereof.

23. A pharmaceutical composition which comprises as an active ingredient a pharmaceutically effective amount of at least one of the compounds as claimed in any prededing claim, and at least one pharmaceutically acceptable inert carrier or diluent.

24. Use of a compound according to Claim 1 as an antimicrobial agent.

25. A process for preparing a compound of the formula:



(I)

wherein R_1 is a hydrogen atom or a lower alkyl group, R_2 is a hydrogen atom or a conventional protecting group for a carboxyl group, R_0 is a hydrogen atom or a conventional protecting group for a hydroxyl group, X is a protected or unprotected amino group, a carboxyl group, a lower alkoxycarbonyl group, an ar(lower)alkyloxycarbonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower alkylthio group, a lower alkylsulfonyl group or a group of either one of the following formulas:

(1) $-CON\begin{matrix}R_3\\R_4\end{matrix}$

wherein R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, or they are taken together to represent an alkylene chain to form, in combination with the adjacent nitrogen atom, a 3- to 7-membered cyclic amino group,

(2) $-ZCOR_5$

wherein Z represents -NH- or -O- and R_5 represents an amino group, a mono(lower)alkylamino group, a di(lower)alkylamino group, a lower alkyloxy group or a lower alkyl group,

(3) $-NH-\underset{\underset{R_6}{|}}{C}=NH$

wherein R_6 represents a hydrogen atom or a lower alkyl group,

(4) $-CH=N-R_7$

wherein R_7 represents a mono(lower)alkylamino group, a di-(lower)alkylamino group or a lower alkyloxy group, or

(5) $-CO-\underset{\underset{R_8}{|}}{N}-N\begin{matrix}R_9\\R_{10}\end{matrix}$

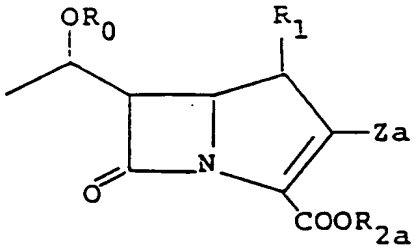
wherein R_8, R_9 and R_{10}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, Y represents a hydrogen atom, a conventinal protecting group for an amino group or a group of either one of the following formulas:

(6) $-CON\begin{matrix}R_{11}\\R_{12}\end{matrix}$

wherein R_{11} and R_{12}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group or

(7) $-\underset{\underset{R_6}{|}}{C}=NE$

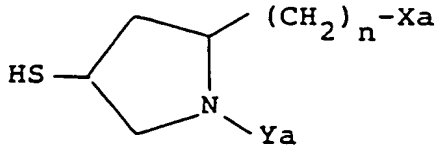
wherein R_6 is as defined above and n is an integer of 1 to 6, which comprises reacting a compound of the formula:



(III)

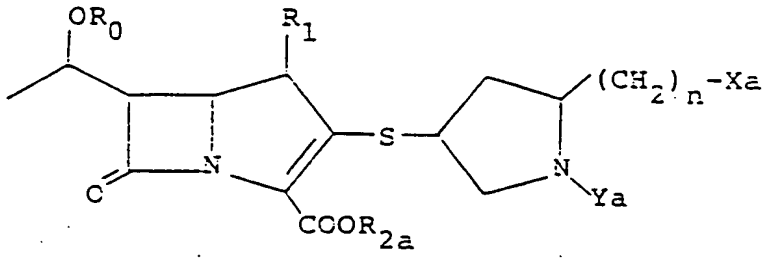
wherein R_0 and R_1 are each as defined above, R_{2a} is a

protecting group for a carboxyl group and Za is a reactive ester group, with a mercaptan of the formula:



(IV)

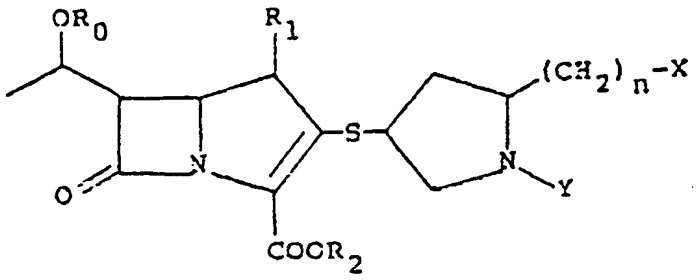
wherein Xa is either one of the groups (1), (2), (4) and (5), a protected amino group, a lower alkoxycarbonyl group, ar(lower)alkoxycarbonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower alkylthio group or a lower alkylsulfonyl group, Ya is a protecting group for an amino group or the group (6) and n is as defined above in the presence of a base in an inert solvent to produce a compound of the formula:



(II)

wherein R_0, R_1, R_{2a}, Xa, Ya and n are each as defined above, optionally followed by removal of the protecting group for the carboxyl group, the protecting group for the hydroxyl group and/or the protecting group for the amino group to give the compound of the formula (II) wherein R_0 and R_{2a} are each a hydrogen atom and/or Ya is a hydrogen atom, or the compound of the formula (II) wherein the protecting group on the group Xa is removed.

26. A process for preparing a compound of the formula:



(I)

wherein R_1 is a hydrogen atom or a lower alkyl group, R_2 is a hydrogen atom or a conventional protecting group for a carboxyl group, R_0 is a hydrogen atom or a conventional protecting group for a hydroxyl group, X is a protected or unprotected amino group, a carboxyl group, a lower alkoxycarbonyl group, an ar(lower)alkyloxycarbonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower alkylthio group, a lower alkylsulfonyl group or a group of either one of the following formulas:

(1) $-CON\begin{matrix}R_3\\R_4\end{matrix}$

wherein R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, or they are taken together to represent an alkylene chain to form, in combination with the adjacent nitrogen atom, a 3- to 7-membered cyclic amino group,

(2) $-ZCOR_5$

wherein Z represents -NH- or -O- and R_5 represents an amino group, a mono(lower)alkylamino group, a di(lower)alkylamino group, a lower alkyloxy group or a lower alkyl group,

(3) $-NH-\underset{\underset{R_6}{|}}{C}=NH$

wherein R_6 represents a hydrogen atom or a lower alkyl group,

(4) $-CH=N-R_7$

wherein R_7 represents a mono(lower)alkylamino group, a di-(lower)alkylamino group or a lower alkyloxy group, or

(5) $-CO-\underset{\underset{R_8}{|}}{N}-N\begin{matrix}R_9\\ \diagdown\\ \diagup\\ R_{10}\end{matrix}$

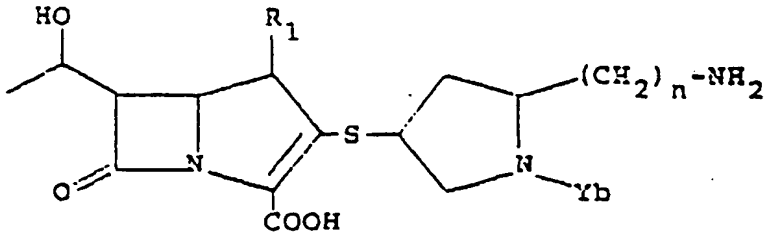
wherein R_8, R_9 and R_{10}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, Y represents a hydrogen atom, a conventinal protecting group for an amino group or a group of either one of the following formulas:

(6) $-CON\begin{matrix}R_{11}\\ \diagdown\\ \diagup\\ R_{12}\end{matrix}$

wherein R_{11} and R_{12}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group or

(7) $-\underset{\underset{R_6}{|}}{C}=NH$

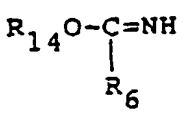
wherein R_6 is as defined above and n is an integer of 1 to 6, which comprises reacting a compound of the formula:



(VI)

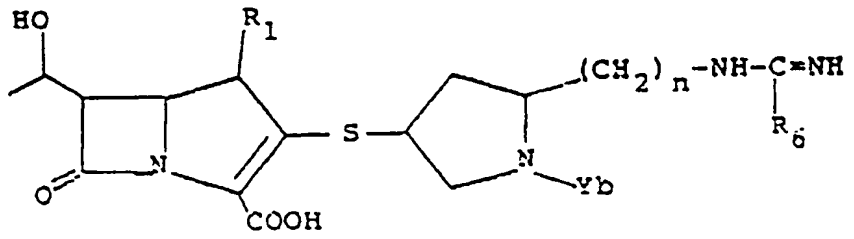
wherein R_1 and n are each as defined above, Yb is the group

(6), with an imine of the formula (8):



(8)

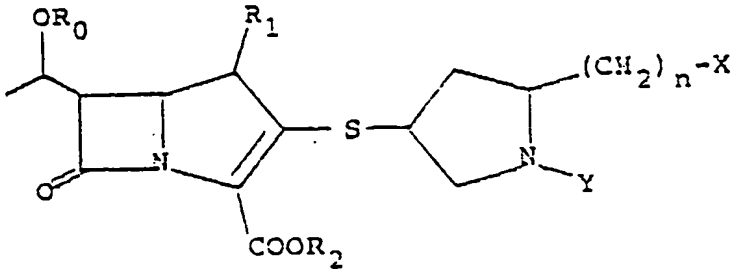
wherein R_6 is as defined above and R_{14} represents a lower alkyl group or a benzyl group, or a salt thereof under a basic condition to produce a beta-lactam compound of the formula:



(V)

wherein R_1, R_6, Yb and n are each as defined above.

27. A process for preparing a compound of the formula:



(I)

wherein R_1 is a hydrogen atom or a lower alkyl group, R_2 is a hydrogen atom or a conventional protecting group for a carboxyl group, R_0 is a hydrogen atom or a conventional protecting group for a hydroxyl group, X is a protected or unprotected amino group, a carboxyl group, a lower alkoxycarbonyl group, an ar(lower)alkyloxycarbonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower

alkylthio group, a lower alkylsulfonyl group or a group of either one of the following formulas:

(1) $-CON\begin{matrix}R_3\\R_4\end{matrix}$

wherein R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, or they are taken together to represent an alkylene chain to form, in combination with the adjacent nitrogen atom, a 3- to 7-membered cyclic amino group,

(2) $-ZCOR_5$

wherein Z represents -NH- or -O- and R_5 represents an amino group, a mono(lower)alkylamino group, a di(lower)alkylamino group, a lower alkyloxy group or a lower alkyl group,

(3) $-NH-\underset{\displaystyle R_6}{\underset{|}{C}}=NH$

wherein R_6 represents a hydrogen atom or a lower alkyl group,

(4) $-CH=N-R_7$

wherein R_7 represents a mono(lower)alkylamino group, a di-(lower)alkylamino group or a lower alkyloxy group, or

(5) $-CO-\underset{\displaystyle R_8}{\underset{|}{N}}-N\begin{matrix}R_9\\R_{10}\end{matrix}$

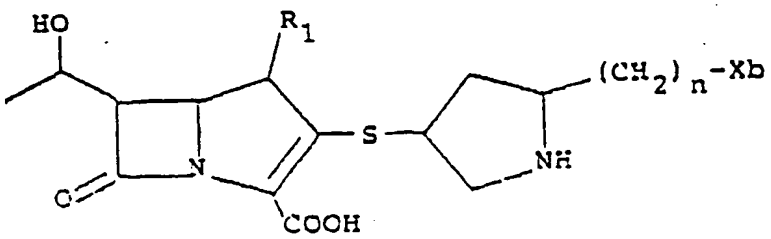
wherein R_8, R_9 and R_{10}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group, Y represents a hydrogen atom, a conventinal protecting group for an amino group or a group of either one of the following formulas:

(6) $-CON\begin{matrix}R_{11}\\R_{12}\end{matrix}$

wherein R_{11} and R_{12}, which may be the same or different, each represents a hydrogen atom or a lower alkyl group or

(7) $-\underset{\displaystyle R_6}{\overset{\displaystyle |}{C}}=NH$

wherein R_6 is as defined above and n is an integer of 1 to 6, which comprises reacting a compound of the formula:

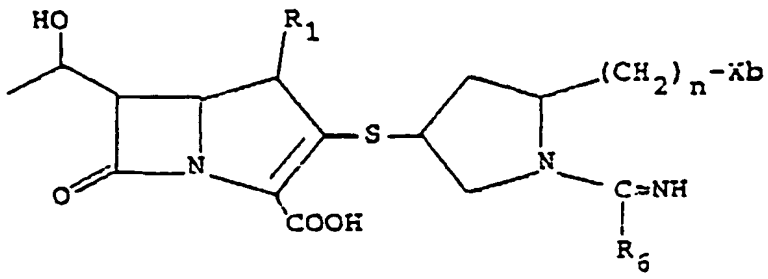


(VIII)

wherein R_1 and n are each as defined above and Xb is either one of the groups (1), (2), (4) and (5), a carboxyl group, a lower alkoxycarbonyl group, a cyano group, a hydroxyl group, a lower alkyloxy group, a lower alkylthio group or a lower alkylsulfonyl group, with an imine of the formula (8):

$$R_{14}O-\underset{\displaystyle R_6}{\overset{\displaystyle |}{C}}=NH \qquad (8)$$

wherein R_6 is as defined above and R_{14} represents a lower alkyl group or a benzyl group, or a salt thereof under a basic condition to produce a beta-lactam compound of the formula (VII):



(VII)

wherein R_1, R_6, Xb and n are each as defined above.

European Patent Office

EUROPEAN SEARCH REPORT

0182213
Application number

EP 85 11 4194

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP-A-0 072 710 (SANKYO) * Claims *	1-3,23-27	C 07 D 487/04 A 61 K 31/40 // C 07 D 207/16 C 07 D 207/12 C 07 D 403/06 C 07 F 7/18
Y	THE JOURNAL OF ANTIBIOTICS, vol. 36, no. 8, August 1983, pages 1034-1039; T. MIYADERA et al.: "Synthesis and in vitro activity of a new carbapenem, RS-533" * Whole document *	1,23-27	(C 07 D 487/04 C 07 D 209:00 C 07 D 205:00)
D,P Y	EP-A-0 126 587 (SUMITOMO) * Claims *	1,23-27	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)
C 07 D 487/00 A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12-02-1986	CHOULY J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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